NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (CDF review of TA600) [ID1683]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (CDF review of TA600) [ID1683]

Contents:

The following documents are made available to consultees and commentators:

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

Pre-technical engagement documents

1. **Company submission summary** from MSD
2. **Clarification questions and company responses**
3. **Evidence Review Group report** prepared by ScHARR
4. **Evidence Review Group report – factual accuracy check**
5. **ERG addendum**
6. **Technical engagement response from company**
   a. Company response
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   a. Dr Yvonne Summers – clinical expert, nominated by MSD
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   a. Royal College of Pathologists
9. **Evidence Review Group critique of company response to technical engagement** prepared by ScHARR
10. **ERG post technical engagement addendum**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA600

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]

Company evidence submission for committee

February 2020

File name	Version	Contains confidential information	Date
MSD Submission Pembrolizumab Combination [ID1683] CDF Review Without Appendices [Redacted]	**1.0**	**Yes**	**27/02/2020**

Instructions for companies

This is the template you should use for your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the Cancer Drugs Fund (CDF) review process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission should not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted.

If applicable provide any supportive and detailed methodological or investigative evidence (additional to the clinical trial and/or Systemic Anti-Cancer Therapy data) in an appendix to this submission.

When cross referring to evidence in the original submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Tables and figures

Cancer Drugs Fund review submission

A.1 Background

As per the Terms of Engagement (ToE) document[1]:

Pembrolizumab with carboplatin and paclitaxel is recommended for use within the Cancer Drugs Fund as an option for untreated metastatic squamous non-small-cell lung cancer (NSCLC). It is recommended only if pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier if disease progresses, and the conditions in the managed access agreement are followed.

- TA531 recommended pembrolizumab monotherapy for PD-L1-positive metastatic non-small-cell lung cancer (NSCLC) for those with a positive PD-L1 expression of 50% or more and is considered the standard of care in this population. For those with a PD-L1 expression of less than 50%, carboplatin plus gemcitabine is the most commonly used chemotherapy regimen, but the committee concluded that all standard chemotherapy treatments can be considered to be of equal efficacy.

·The key clinical evidence was taken from the phase III trial KEYNOTE-407.

- At the most recent data cut (April 2018), median overall survival was 15.9 months for pembrolizumab combination therapy and 11.3 months for standard chemotherapy (hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.49 to 0.85). Median follow-up was 7.8 months.

- The committee considered that the survival evidence was uncertain given the immaturity of the data presented.

- Subgroup analyses based on tumour proportion score were not robust enough for decision making.

- The committee were aware that the final data cut in the trial would be available in [redacted] and provide an additional [redacted] of follow-up. The committee concluded that this had the potential to resolve the key uncertainties in the survival estimates.

Please note, as per the information communicated at the kick off meeting, the final analysis data base lock of the trial was in [redacted], therefore an additional [redacted] months of data has been collected.

A.2 Key committee assumptions

Area	Committee discussion and preferred assumptions
Population	• Adults with untreated, metastatic, squamous non-small-cell lung cancer (NSCLC)
Comparators	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab monotherapy (only in PD-L1-positive NSCLC if the tumour expresses at least a 50% tumour proportion score)
Comparative evidence	• KEYNOTE-407 compares pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel with placebo plus carboplatin and paclitaxel or nab-paclitaxel in adults with untreated advanced or metastatic squamous NSCLC with an Eastern Cooperative Oncology Group performance status of 0 or 1 • The committee concluded all standard chemotherapy treatments can be considered to be of equal efficacy, and therefore KEYNOTE-407 was relevant for decision making for this population • The company performed an indirect treatment comparison to compare pembrolizumab combination with pembrolizumab monotherapy for people whose tumours express PD-L1 with at least a 50% tumour proportion score o Median overall survival was not reached for the PD-L1 tumour proportion score of 50% or higher subgroup in either arm of KEYNOTE-407 o The hazard ratio for the comparison was 0.97 (95% CI 0.50 to 1.89) o The committee concluded that the outputs from the indirect treatment comparison were not robust enough for decision making • The subgroup analysis of those with a tumour proportion score of lower than 50% is not robust enough for decision making

	○ The same extrapolation method as the ITT population was applied to estimate overall survival for the PD-L1 subgroups. These extrapolations may not be the most appropriate for subgroup analyses ○ In addition, the ERG's clinical advisers could not give survival estimates by PD-L1 tumour proportion score because it was too uncertain
Model structure	• The company's model structure is appropriate for decision making
Stopping rule	• 2 year stopping rule is appropriate given current available evidence but should be reviewed in light of new evidence
Extrapolation of overall survival	• Modelling used the SEER database is not appropriate for decision making because it does not include second-line immunotherapy treatments • A log-logistic model with no cut point for both treatment arms, is more appropriate for decision making when considering the overall population • It is currently unclear what extrapolation is most appropriate for any subgroup analyses, as evidence presented to committee was not robust enough for decision-making
Subsequent treatment	• 50% of people in the standard care arm would be offered subsequent treatments (of these, 75% would have atezolizumab and 25% would have pembrolizumab
Utilities	• Preference to use progression-based approach: pre-progression utility value from KEYNOTE-407 and a post-progression value (0.58) from the TOPICAL trial (Khan et al. 2014)
Duration of treatment effect	• Lifetime treatment effect for pembrolizumab combination therapy was not considered to be plausible because there was no evidence to suggest this duration of benefit ○ The ERG log-logistic model did not include an explicit treatment effect but did include a varying hazard ratio over time because the parametric extrapolations were chosen to match their clinical adviser estimates

End of life	• The committee noted that its preferred ERG model estimates that, for the overall population (that is, irrespective of PD-L1 status), people currently live for on average 2.17 years on chemotherapy. This exceeds the normal maximum that is considered a short life expectancy (24 months) • The committee considered that those with TPS ≥50% may live for longer than that estimated by the model as they would be able to take pembrolizumab monotherapy. However, the committee used the overall population for decision-making because the evidence for this subgroup was unsuitable • The committee heard from the clinical experts that the end-of-life criteria had been met for non-squamous NSCLC in previous appraisals, and that squamous NSCLC tends to have a poorer prognosis • Based on the current comparative evidence presented, the committee concluded pembrolizumab with carboplatin and paclitaxel might meet the end-of-life criteria • The committee noted that because the interim trial data were of very short duration, the modelled estimates were based on very immature data. It considered it was plausible that further evidence presented at the end of the data collection period, specifically the comparator arm of KEYNOTE-407, would provide more reliable evidence on whether those with untreated metastatic squamous NSCLC (or subgroups within that population) had a life expectancy of less than 24 months.

A.3 Other agreed changes

- Where requested changes to the model impact other assumptions, these may also be updated, but should be explicitly highlighted to NICE and the committee. e.g. updating other survival inputs (i.e. progression-free survival) in addition to overall survival.

- NICE and the Evidence Review Group may request further data to be provided or analyses to be conducted during critique of the evidence if they consider it necessary for committee decision-making.

- The company should not make alter the decision-problem, submit additional evidence or make further alterations to the model during the CDF review period unless NICE requests or agrees to this in advance.

A.4 The technology

Table 1 Technology being reviewed

UK approved name and brand name	Pembrolizumab (KEYTRUDA®) in combination with pemetrexed and platinum chemotherapy (pembrolizumab combination)
Mechanism of action	Pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment[2]
Marketing authorisation/CE mark status	The indication to which this submission relates to is as follows: **Keytruda, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.** The above indication was approved as a Type II variation via the EMA's Centralised Procedure. The date of the CHMP opinion was 31st January 2019[3].
Indications and any restriction(s) as described in the summary of product characteristics	The Marketing Authorisation for Pembrolizumab also currently covers the following indications [2]: • KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. • KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection. • KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. • KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.

	• KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA. • KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10. • KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy. • KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.
Method of administration and dosage	The recommended dose of KEYTRUDA as part of combination therapy is 200 mg every 3 weeks administered as an intravenous infusion over 30 minutes[2]
Additional tests or investigations	For the indication under consideration, no diagnostic test is required to identify the population for whom pembrolizumab is indicated.
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100mg vial. The mean treatment duration per patient including the CDF follow up period was [redacted] days. Based on 200mg every 3 weeks, this equates to an average cost of a course of treatment at list price of £[redacted] (no. of cycles x cost per cycle)([redacted] x (2 x 2,630))[4]

	The maximum treatment duration would be 2 years.
Commercial arrangement (if applicable)	Currently a simple discount patient access scheme (PAS) is operational for all pembrolizumab indications approved through baseline commissioning. The providers will purchase pembrolizumab from MSD and MSD will supply the same at its confidential NHS net discount price for all indications; at a [redacted] discount on MSD's list price, plus VAT, where applicable. This discount would apply to the indication covered by this submission upon successful exit from the CDF in baseline commissioning.
Date technology was recommended for use in the CDF	September, 2019
Data collection end date	[redacted]

A.5 Clinical effectiveness evidence

Table 2 Primary source of clinical effectiveness evidence

Study title	**KEYNOTE-407**
Study design	KEYNOTE-407 is a phase 3, worldwide, randomized, placebo controlled with active treatment, parallel group, multi-site, double blind study of pembrolizumab combined with carboplatin and paclitaxel (or nab-paclitaxel) versus saline placebo combined with carboplatin and paclitaxel (or nab-paclitaxel) in participants with untreated metastatic squamous NSCLC[5]
Population	Adults with untreated, metastatic, squamous NSCLC [5]
Intervention(s)	Pembrolizumab with carboplatin and paclitaxel/nab-paclitaxel
Comparator(s)	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) As discussed, and agreed at the kick off meeting, the results presented in A.6 compare the intervention to placebo plus carboplatin and paclitaxel/nab-paclitaxel. The intervention will not be compared versus other chemotherapy regimens via means of a network meta-analysis (NMA) please see A.7 for the rationale. • Pembrolizumab monotherapy (only in PD-L1-positive NSCLC if the tumour expresses at least a 50% tumour proportion score)
Outcomes collected that address committee's key uncertainties	• **Overall Survival (OS)** **Progression-Free Survival (PFS)** and **Time on Treatment (ToT)** were outcomes also collected to be included in the economic model.
Reference to section in appendix	A.6.

A.6 Key results of the data collection

The clinical data presented in this submission are from the final analysis (FA) of the KEYNOTE-407 clinical trial, based on a data cut-off date of 09th May 2019 [6](database lock date of [redacted]), to support this submission to NICE for the CDF guidance review of TA600 [7].
All efficacy analyses were conducted using the intention to treat (ITT) population. At the FA data cut-off date, patients had a median duration of follow-up of 14.3 months, an additional 6.5 months compared to the submission presented at the point of CDF entry.
The key results presented below are for the pembrolizumab combination versus standard of care (SoC) in the ITT population, PD-L1 TPS <1%, PD-L1 TPS 1-49% and PD-L1 TPS ≥50% subgroups to address the key clinical uncertainty highlighted in the data collection agreement (DCA) [8].

A.6.1 *Overall survival - ITT Population*

Table 3 and Table 4 present OS analysis results and Figure 1 presents the Kaplan-Meier (KM) estimates of OS. As with the submission at the point of CDF entry, a statistically significant higher OS was reported in the pembrolizumab combination arm compared with the control (HR 0.71; 95% CI: 0.58, 0.88; p<[redacted])[6, 9].

Median OS in the pembrolizumab combination arm was 17.1 months compared with 11.6 months in the control (Table 3). The OS rate was higher at 6 months, and remained higher at [redacted] months ([redacted]% vs [redacted]%), [redacted] months ([redacted]% vs [redacted]%) and [redacted] months ([redacted]% vs [redacted]%) (Table 4). Figure 1 demonstrates the pembrolizumab combination curve separated from the control curve early at month 2, with continuous separation over time[9].

At data cut-off, the proportion of patients discontinuing treatment that received post-discontinuation therapy in the control arm was [redacted]%. This included [redacted] eligible patients with disease progression had crossed over to pembrolizumab monotherapy within the study and an additional [redacted] patients received a subsequent therapy outside of the study protocol. Despite this high rate of patients receiving post discontinuation therapy the clinically meaningful OS benefit persisted (Table 19)[10].

Table 3. Analysis of OS - ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembro Combo	278	168 (60.4)	[redacted]	[redacted]	17.1 (14.4, 19.9)	83.5 [redacted]	0.71 (0.58, 0.88)	[redacted]
Control	281	197 (70.1)	[redacted]	[redacted]	11.6 (10.1, 13.7)	75.6 [redacted]	---	---

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

‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).

‡‡ One-sided p-value based on stratified log-rank test.

Database Cutoff Date: 09MAY2019

Source: [9]

Table 4. Summary of OS Rate Over Time

	Pembro Combo (N=278) % (95% CI)†	Control (N=281) % (95% CI)†
Summary of Overall Survival rate at time point		
6 months	83.5 [redacted]	75.6 [redacted]
9 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

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

Database cutoff date: 09MAY2019

Source: [9]

Figure 1. Kaplan Meir Estimates of OS - ITT Population

Source:[9]

A.6.2 *Overall survival – by PD-L1 Expression*

The OS benefit of the pembrolizumab combination over the control was observed across all PD-L1 expression subgroups TPS <1%, TPS 1-49%, and TPS ≥50%, following a similar trend in risk reduction with that of the data presented at the point of CDF entry. The HRs of 0.79, 0.59 and 0.79 were reported across PD-L1 TPS <1%, TPS 1-49%, and TPS ≥50%, respectively (Figure 2) [9 6].

Median OS was longer in the pembrolizumab combination than control in each of the PD-L1 expression subgroups: TPS <1% ([redacted] vs [redacted] months), TPS 1 to 49% ([redacted] vs [redacted] months) and TPS ≥50% subgroup ([redacted] vs [redacted] months) (Table 5, Table 6 and Table 7) [9].

As with the submission at the point of CDF entry, the KM curves for all PD-L1 subgroups demonstrated a consistent effect of pembrolizumab combination over control, regardless of PD-L1 expression status. The KM curves separated earlier as PD-L1 increased (after 7 months for TPS <1%, after 2 months for 1-49%, and at Month 0 for TPS ≥50%) (Figure 3, Figure 4 and Figure 5)[9].

Figure 2. Forest Plot of OS Hazard Ratio by PD-L1 Expression - ITT Population

Source: [9]

Table 5. Analysis of OS - ITT Populations, TPS <1%

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembro Combo	95	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.79 (0.56, 1.11)	[redacted]
Control	99	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	---	---

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

‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).

‡‡ One-sided p-value based on stratified log-rank test.

Database Cutoff Date: 09MAY2019

Source: [9]

Figure 3. Kaplan-Meier Estimates of OS - ITT Population, TPS <1%

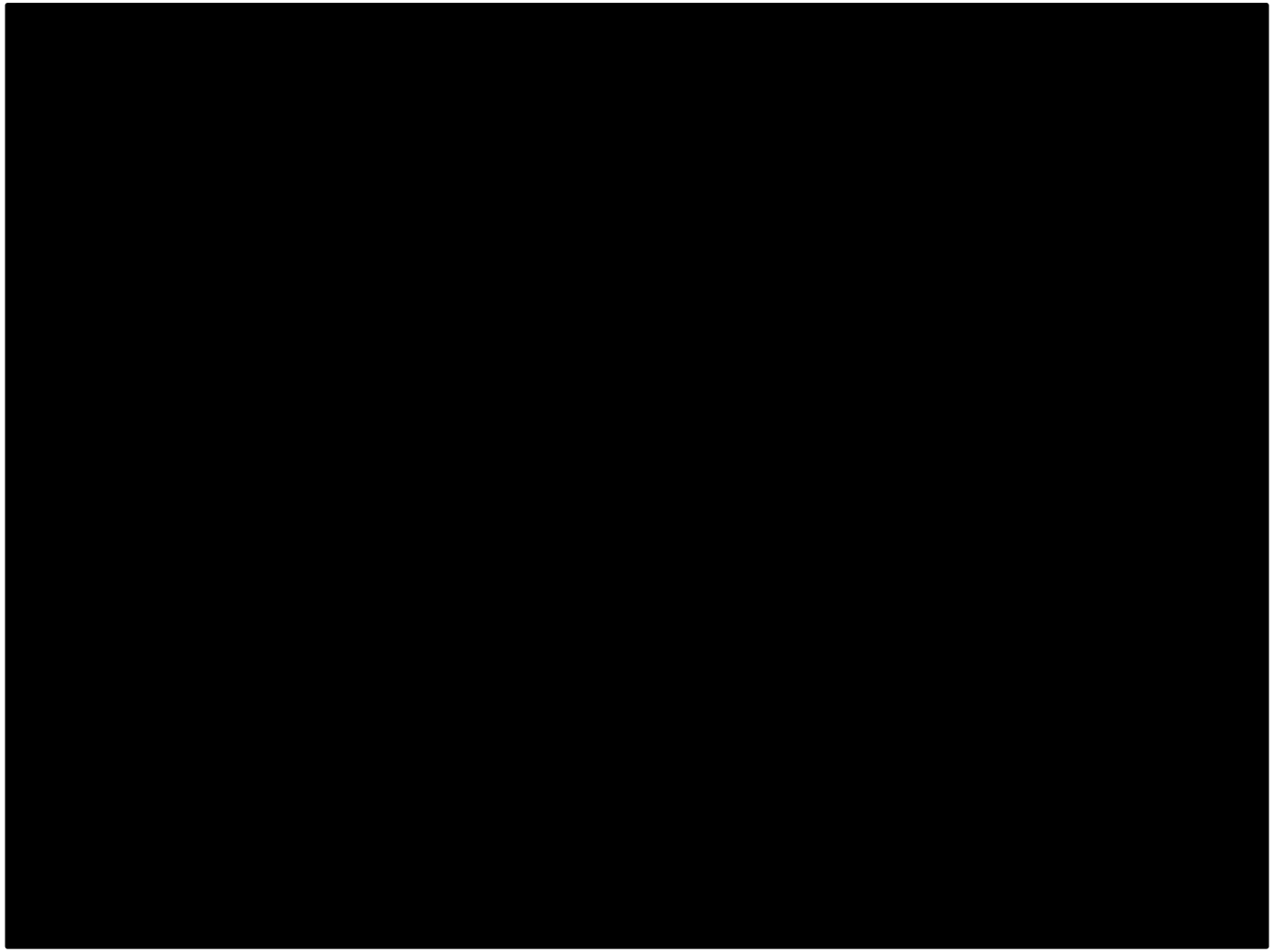


Table 6. Analysis of OS - ITT Population, TPS 1-49%

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	OS Rate at Month 6 in %[†] (95% CI)	vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‡‡]
Pembro Combo	103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.59 (0.42, 0.84)	[redacted]
Control	104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	---	---

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

[‡] Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).

[‡‡] One-sided p-value based on stratified log-rank test.

Database Cutoff Date: 09MAY2019

Source:

Figure 4. Kaplan Meier Estimates of OS - ITT Population, TPS 1-49%

Source: [9]

Table 7. Analysis of OS - ITT Population, TPS ≥50%

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	OS Rate at Month 6 in %[†] (95% CI)	vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‡‡]
Pembro Combo	73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.79 [redacted]	[redacted]
Control	73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	---	---

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

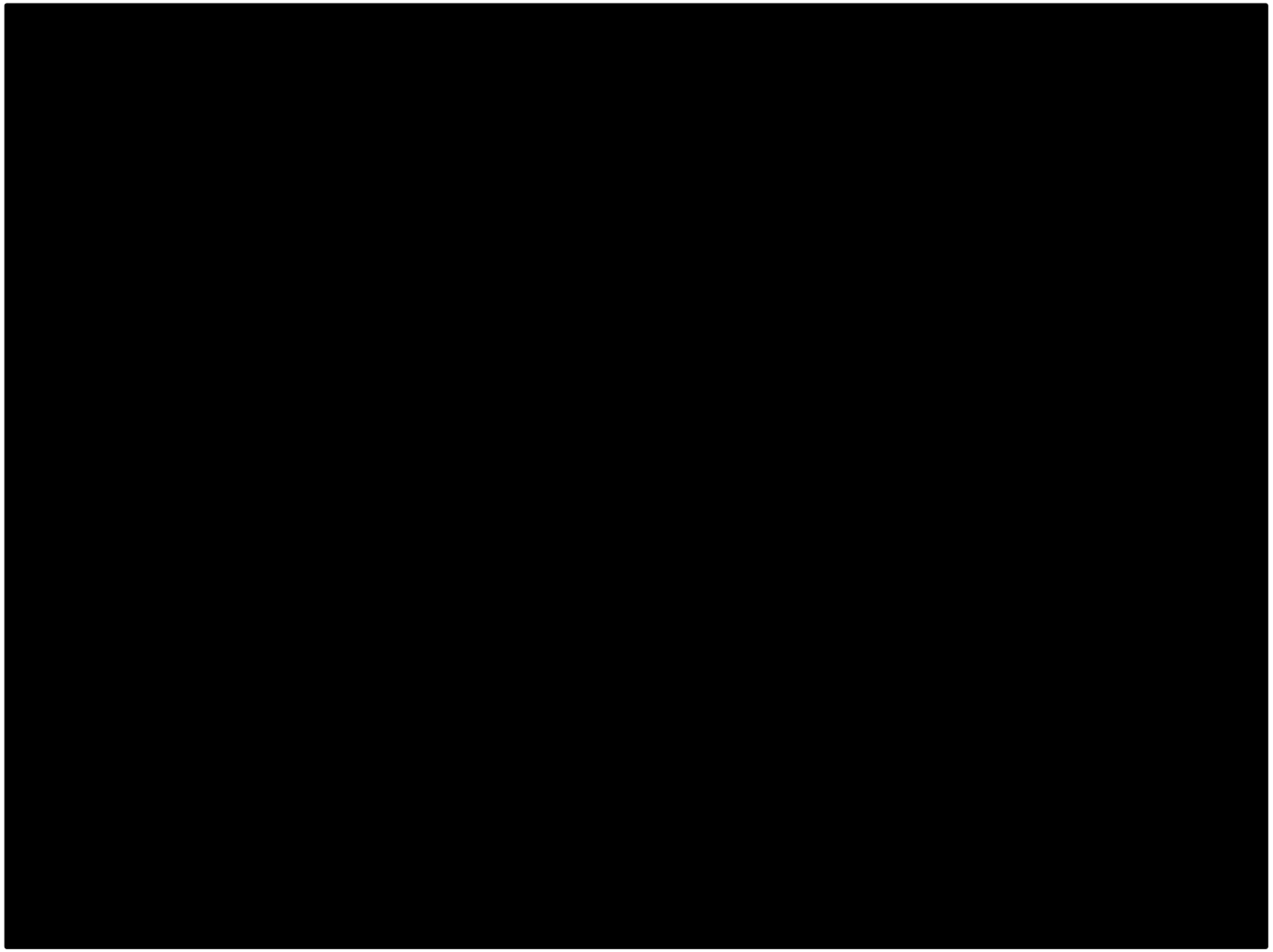
[‡] Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).

[‡‡] One-sided p-value based on stratified log-rank test.

Database Cutoff Date: 09MAY2019

Source: [9]

Figure 5. Kaplan Meier Estimates of OS - ITT Population, TPS ≥50%



Source:[9]

A.6.3 *Progression Free Survival – ITT Population*

Table 8 and Table 9 present the results of the PFS analysis and Figure 6 presents the KM estimates of PFS. As per the data submitted with the submission at point of CDF entry, a statistically significant and clinically meaningful benefit in PFS was seen for the pembrolizumab combination compared with control based on blinded independent central review (BICR) assessment (HR 0.57; 95% CI: 0.47, 0.69; p<[redacted]) (**Error! Reference source not found.**)[6, 9].

Median PFS for pembrolizumab combination was 8 months compared with 5.1 months for the control (Table 8). The PFS benefit for the pembrolizumab combination was higher vs the control at 6 months and remained higher at [redacted] months ([redacted]% vs [redacted]%), [redacted] months ([redacted]% vs [redacted]%) and [redacted] months [redacted]% vs [redacted]%) (Table 9). The KM plot for PFS based on BICR assessment demonstrated that the pembrolizumab combination curve separated early from the control curve at Week 6 and was sustained throughout the remainder of the evaluation period Figure 6 [9].

As per the KEYNOTE-407 study protocol, sensitivity analyses were performed for comparison of PFS based on investigator assessment (rather than BICR) per RECIST 1.1. Results of the sensitivity analyses are presented in Appendix 2 and are consistent with the results of the primary analysis of PFS presented below [9].

Table 8. Analysis of PFS Based on BICR Assessment per RECIST 1.1 - ITT Population

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembro Combo	278	217 (78.1)	[redacted]	[redacted]	8.0 (6.3, 8.4)	65.6 [redacted]	0.57 (0.47, 0.69)	[redacted]
Control	281	252 (89.7)	[redacted]	[redacted]	5.1 (4.3, 6.0)	44.9 [redacted]	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

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

‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).

‡‡ One-sided p-value based on stratified log-rank test.

Database Cutoff Date: 09MAY2019

Source: [9]

Table 9. Summary of PFS Over Time Based on BICR per RECIST 1.1 - ITT Population

	Pembro Combo (N=278) % (95% CI)†	Control (N=281) % (95% CI)†
Summary of PFS rate at time point		
6 months	65.6 [redacted]	44.9 [redacted]
9 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

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

BICR = Blinded independent central review.

Database cutoff date: 09MAY2019

Source: [9]

Figure 6. Kaplan-Meier Estimates of Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 - ITT Population

Source: [9]

A.6.4 *Progression Free Survival – by PD-L1 Expression*

Similarly to the submission at the point of CDF entry, the PFS benefit of the pembrolizumab combination over the control was observed across all PD-L1 expression subgroups TPS <1%, TPS 1-49%, and TPS ≥50%, with HRs of 0.67, 0.52 and 0.43 respectively (Figure 7). As per the data submitted at the point of CDF entry, an incremental PFS benefit was observed with increased PD-L1 expression [6, 9].

Median OS was longer in the pembrolizumab combination than control in each of the PD-L1 expression subgroups: TPS <1% (vs months), TPS 1 to 49% (vs months) and TPS ≥50% subgroup (vs) (Table 10, Table 11 and Table 12[9]).

The KM curves for all PD-L1 subgroups analysed demonstrated a consistent beneficial effect of pembrolizumab combination over the control arm, regardless of PD-L1 expression status. The PFS KM curves for the two treatment groups separated early and remained separated throughout the evaluation period, with the KM curves separating earlier as PD-L1 expression levels increased (after months for TPS <1%, after months for 1-49%, and at Month for TPS ≥50%) (Figure 8, Figure 9 and Figure 10) [9].

Figure 7. Forest Plot of PFS Hazard Ratio by PD-L1 Expression Based on BICR Assessment per RECIST 1.1- ITT Population

Source: [9]

Table 10. Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 - ITT Population, TPS<1%

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembro Combo	95	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.67 (0.49, 0.91)	[redacted]
Control	99	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

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

‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).

‡‡ One-sided p-value based on stratified log-rank test.

Database Cutoff Date: 09MAY2019

Source: [9]

Figure 8. Kaplan-Meier Estimates of Progression-Free-Survival- Based on BICR Assessment per RECIST 1.1 - ITT Population, TPS<1%

Source: [9]

Table 11. Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 - ITT Population, TPS 1-49%

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembro Combo	103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.52 (0.38, 0.71)	[redacted]
Control	104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

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

‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).

‡‡ One-sided p-value based on stratified log-rank test.

Database Cutoff Date: 09MAY2019

Source: [9]

Figure 9. Kaplan-Meier Estimates of Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 - ITT Population, TPS 1-49%

Source: [9]

Table 12. Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 - ITT Population, TPS≥50%

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembro Combo	73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.43 (0.29, 0.63)	[redacted]
Control	73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	---	---

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

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

‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).

‡‡ One-sided p-value based on stratified log-rank test.

Database Cutoff Date: 09MAY2019

Source:[9]

Figure 10. Kaplan-Meier Estimates of Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 - ITT Population, TPS≥50%

Source:[9]

A.6.5 *Time of Treatment*

The duration of exposure, measured from the date of the first dose to the date of the last dose of treatment, for the all subjects as treated (ASaT) population is presented in Table 13. Similarly, to the submission at the time of CDF entry, the time on treatment was longer for the pembrolizumab combination compared with the control for the ASaT population (Table 13) and irrespective of PD-L1 TPS subgroup (TPS <1%, TPS 1-49% and TPS ≥50%) (Table 14, Table 15, and Table 16)[4].

Median duration of exposure was [redacted] days (SD [redacted] days) in the pembrolizumab combination arm compared with [redacted] days (SD [redacted] days) in the control. The mean number of cycles of treatment received was [redacted] (SD [redacted]) and [redacted] (SD [redacted]) in the pembrolizumab combination and control groups respectively (Table 13)[4].

Corresponding to the original submission, in participants who received carboplatin/paclitaxel as chemotherapy, a slightly higher proportion in the pembrolizumab combination group completed all 4 cycles of carboplatin and paclitaxel compared with the control (Table 17). In the carboplatin/nab-paclitaxel treated population, similar proportions of participants in the pembrolizumab combination and the control completed the 4 cycles of carboplatin and 4 cycles (12 administrations) of nab-paclitaxel (Table 18). As expected, participants in the pembrolizumab combination group received more cycles of pembrolizumab compared with those in the control receiving the placebo, indicating a longer duration on treatment. This was observed with both chemotherapy regimens.

Table 13. Summary of Drug Exposure of any study treatment component (ASaT Population)

	Pembro Combo (N=278)	Control (N=280)
Number of Days on Therapy		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Number of Cycles		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Database Cutoff Date: 09MAY2019		

Source:[4]

Table 14. Summary of Drug Exposure of any study treatment component (ASaT Population, TPS<1%)

	Pembro Combo (N=95)	Control (N=99)
Number of Days on Therapy		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Number of Cycles		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Database Cutoff Date: 09MAY2019		

Source:[4]

Table 15. Summary of Drug Exposure of any study treatment component (ASaT Population, TPS 1-49%)

	Pembro Combo (N=103)	Control (N=103)
Number of Days on Therapy		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Number of Cycles		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Database Cutoff Date: 09MAY2019		

Source:[4]

Table 16. Summary of Drug Exposure of any study treatment component (ASaT Population, TPS ≥50%)

	Pembro Combo (N=73)	Control (N=73)
Number of Days on Therapy		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Number of Cycles		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Database Cutoff Date: 09MAY2019		

Source:[4]

Table 17. Summary of Drug Administration by Dose Regimen (ASaT Population – Carboplatin/Paclitaxel)

Number of Administrations	Pembro Combo (N = 169)			Control (N = 167)		
	Pembrolizumab n (%)	Paclitaxel n (%)	Carboplatin n (%)	Placebo n (%)	Paclitaxel n (%)	Carboplatin n (%)
Subjects with at least one administration of the drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For subjects who crossed over to pembrolizumab from the Control Group, doses administered after crossover are excluded.
Subjects with at least one administration of the drug will be taken as the denominator.
The maximum allowed number of administrations for carboplatin and paclitaxel is 4.
Database Cutoff Date: 09MAY2019

Source:[4]

Table 18. Summary of Drug Administration by Dose Regimen (ASaT Population – Carboplatin/Nab-Paclitaxel)

Number of Administrations	Pembro Combo [redacted]			Control [redacted]		
	Pembrolizumab n (%)	Nab-Paclitaxel n (%)	Carboplatin n (%)	Placebo n (%)	Nab-Paclitaxel n (%)	Carboplatin n (%)
Subjects with at least one administration of the drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For subjects who crossed over to pembrolizumab from the Control Group, doses administered after crossover are excluded.
Subjects with at least one administration of the drug will be taken as the denominator.
The maximum allowed number of administrations for carboplatin is 4. The maximum allowed number of administrations for nab-paclitaxel is 12.
Database Cutoff Date: 09MAY2019

Source:[4]

A.6.6 *Subsequent therapies*

During the appraisal at the point of CDF entry, the ERG considered there to be uncertainty surrounding the expected long-term survival of patients receiving pembrolizumab combination or SoC, including those patients who go onto receive subsequent therapies. Therefore, it was agreed at the kick-off meeting, with NICE and the ERG, that the proportion and duration of subsequent therapies received in each arm would be presented (Table 19 and Table 20).

Table 19. Utilization of New Oncologic Therapies after Discontinuing from Study Treatment (All-Subjects-as-Treated Population)

Study: 3475-407	**Patients with new therapy**	
Line **Therapy**	**Pembro Combo** **N = 278**	**Control** **N = 280**
Patients with one or more lines of therapy	[redacted]	[redacted]
2L	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]
gemcitabine	[redacted]	[redacted]
docetaxel	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]
carboplatin + gemcitabine	[redacted]	[redacted]
cisplatin + gemcitabine	[redacted]	[redacted]
carboplatin + paclitaxel	[redacted]	[redacted]
docetaxel + ramucirumab	[redacted]	[redacted]
gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]
vinorelbine tartrate	[redacted]	[redacted]
carboplatin + paclitaxel albumin	[redacted]	[redacted]
cisplatin	[redacted]	[redacted]
etoposide	[redacted]	[redacted]
atezolizumab	[redacted]	[redacted]
cisplatin + docetaxel	[redacted]	[redacted]
cisplatin + vinorelbine tartrate	[redacted]	[redacted]
gemcitabine + vinorelbine tartrate	[redacted]	[redacted]
cancer CEA HER2 MAGE2 MAGE3 p53 DNA vaccine	[redacted]	[redacted]
carboplatin + cisplatin + docetaxel + etoposide	[redacted]	[redacted]
carboplatin + cisplatin + gemcitabine	[redacted]	[redacted]
carboplatin + gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]
cisplatin + gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]
docetaxel + investigational drug (unspecified)	[redacted]	[redacted]
gemcitabine + nedaplatin	[redacted]	[redacted]
gemcitabine hydrochloride + nedaplatin	[redacted]	[redacted]
hydrazine sulfate	[redacted]	[redacted]
investigational drug (unspecified)	[redacted]	[redacted]
nedaplatin + paclitaxel	[redacted]	[redacted]
nedaplatin + vascular endothelial growth factor inhibitor (unspecified) + v	[redacted]	[redacted]
paclitaxel	[redacted]	[redacted]
strontium chloride Sr 89	[redacted]	[redacted]
3L	[redacted]	[redacted]
docetaxel	[redacted]	[redacted]
gemcitabine	[redacted]	[redacted]
vinorelbine tartrate	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]
cisplatin + gemcitabine	[redacted]	[redacted]

docetaxel + ramucirumab	[redacted]	[redacted]
carboplatin + gemcitabine	[redacted]	[redacted]
paclitaxel	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]
atezolizumab	[redacted]	[redacted]
gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]
carboplatin + gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]
carboplatin + paclitaxel	[redacted]	[redacted]
bevacizumab + pemetrexed disodium	[redacted]	[redacted]
capecitabine + oxaliplatin	[redacted]	[redacted]
carboplatin + docetaxel	[redacted]	[redacted]
carboplatin + paclitaxel albumin	[redacted]	[redacted]
cisplatin + pemetrexed disodium	[redacted]	[redacted]
cisplatin + vinorelbine tartrate	[redacted]	[redacted]
etoposide	[redacted]	[redacted]
gemcitabine + nedaplatin	[redacted]	[redacted]
gimeracil (+) oteracil potassium (+) tegafur + nedaplatin	[redacted]	[redacted]
hydrazine sulfate	[redacted]	[redacted]
nintedanib	[redacted]	[redacted]
nivolumab + paclitaxel albumin	[redacted]	[redacted]
pemetrexed disodium	[redacted]	[redacted]
4L	[redacted]	[redacted]
vinorelbine tartrate	[redacted]	[redacted]
docetaxel	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]
gemcitabine	[redacted]	[redacted]
gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]
afatinib	[redacted]	[redacted]
atezolizumab	[redacted]	[redacted]
bevacizumab + paclitaxel albumin	[redacted]	[redacted]
carboplatin	[redacted]	[redacted]
carboplatin + gemcitabine	[redacted]	[redacted]
carboplatin + gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]
cisplatin + gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]
erlotinib hydrochloride	[redacted]	[redacted]
irinotecan hydrochloride	[redacted]	[redacted]
5L	[redacted]	[redacted]
atezolizumab	[redacted]	[redacted]
cisplatin + gemcitabine hydrochloride	[redacted]	[redacted]
docetaxel + ramucirumab	[redacted]	[redacted]
gefitinib	[redacted]	[redacted]
gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]
lysine-specific histone demethylase 1 inhibitor (unspecified)	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]
paclitaxel	[redacted]	[redacted]
vinorelbine tartrate	[redacted]	[redacted]
6L	[redacted]	[redacted]
docetaxel	[redacted]	[redacted]
docetaxel + ramucirumab	[redacted]	[redacted]
paclitaxel albumin	[redacted]	[redacted]
7L	[redacted]	[redacted]
gemcitabine	[redacted]	[redacted]
8L	[redacted]	[redacted]
gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]

2L includes pembrolizumab monotherapies from subjects who crossed over from control group to pembro mono treatment allowed by protocol

(Database Cutoff Date: 09MAY2019).

Source: {Merck Data on File, 2019 #140}

Table 20. Duration of New Oncologic Therapies Per Therapy Type per Line in Days Subjects Who Discontinued or Completed Study Treatment (All-Subjects-as-Treated Population)

Treatment Duration† (Days)	Pembro Combo (N=238)		Control (N=275)		Pooled (N=513)	
	n (%)‡	Mean (SE)	n (%)‡	Mean (SE)	n (%)‡	Mean (SE)
Subjects With One or More New Oncologic Therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Anti-PD1/PD-L1 Therapies Only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Chemotherapies Only or Combined Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Other Therapies Only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Anti-PD1/PD-L1 Therapies Only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Both Anti-PD1/PD-L1 Therapies and Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1/PD-L1 Therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Chemotherapies Only or Combined Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Other Therapies Only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Anti-PD1/PD-L1 Therapies Only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Chemotherapies Only or Combined Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Anti-PD1/PD-L1 Therapies Only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Chemotherapies Only or Combined Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Other Therapies Only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Chemotherapies Only or Combined Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Chemotherapies Only or Combined Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjects Who Received Chemotherapies Only or Combined Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Treatment duration is defined as the days from start date of the treatment until the stop date of treatment, or until censoring date of overall survival if the stop date is not available, or until the database cutoff date for the treatment initiated after the censoring data of overall survival. For subsequent therapy which consists of multiple drugs from the same type of treatment components, the average of the treatment duration is first calculated within the subsequent therapy. For subjects who crossed over from control group to pembro mono treatment, the treatment duration, which is the number of days from the date of first dose till the date of last dose of pembrolizumab during cross over period, is reported as second line treatment.

‡ Every subject is counted a single time for each applicable row and column.

‖ Anti-PD1/PD-L1 Treatment refers to the therapy using atezolizumab, cemiplimab, durvalumab, nivolumab, pembrolizumab.

For combined chemotherapies, only the treatment duration of the chemotherapy components is considered

A category of therapy type appears on this table only if its incidence in one or more of the columns is greater than 0.

Database cutoff date: 09MAY2019

Source: {Merck Data on File, 2019 #1403}

A.7 Evidence synthesis

As agreed at the kick of meeting with NICE and the ERG, MSD will not be presenting a comparison of pembrolizumab combination with other chemotherapy treatments (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) by means of a NMA or an updated systematic literature review (SLR).

Clinical advisors to the ERG, during the appraisal at the point of CDF entry, agreed that the platinum-based chemotherapy regiments have very similar efficacy for the population of interest [11]. In addition, clinical experts consulted by MSD during the appraisal at the point of CDF entry were in agreement, that the chemotherapy regimens are of comparable efficacy, citing a publication by Treat et al, [12]. Therefore, during the technical engagement of the appraisal, TA600, it was concluded that all standard chemotherapy treatments can be considered to be of equal efficacy, and therefore KEYNOTE-407 was relevant for decision making for this population[13].

Furthermore, during the appraisal of TA411, the committee agreed with clinical experts in that platinum-based regimens (gemcitabine, vinorelbine, docetaxel or paclitaxel) were all very similar in efficacy in previously untreated advanced squamous NSCLC [14]. This consensus has also been reported in a paper by Schiller et al, which describes a comparison of four platinum base chemotherapy regimens for advanced NSCLC concludes, “none of the four chemotherapy regimens offered a significant improvement over the others”[15]. Hence, based on the above rationale, it is not necessary nor relevant to provide an updated NMA since the comparator in the KEYNOTE-407 trial is the most applicable to UK clinical practice and the comparison of pembrolizumab combination with the SoC will be reported in the FA results presented in this current submission.

A.7.1 *Indirect Treatment Comparison [16]*

The results of the indirect treatment comparison (ITC) of pembrolizumab + chemotherapy (KEYNOTE-407) versus pembrolizumab monotherapy (KEYNOTE-042) under proportional hazards were reported in the submission at the point of CDF entry. However, further investigation was conducted to examine the proportional hazard (PH) assumption for the FA data cut presented in this current submission. Statistical testing revealed a departure from a PH assumption for hazard ratios for the ITC and therefore time-varying HRs were assumed in the model for the comparison of pembrolizumab combination versus pembrolizumab monotherapy. Assessment of the PH assumption consisted of both graphical inspection and test of scaled Schoenfeld residuals after fitting the model as proposed by Grambsch and Therneau.

More flexible parametric alternative approaches that relax the PH assumption and accommodate variation of treatment effect over time were considered as sensitivity analyses in order:

- To evaluate consistency of findings when PH assumption is relaxed,

- To inform on the time course treatment effect in each arm and the variation of the relative treatment effect over time.

These parametric models specified the hazard rates as a function of time (e.g. Log hazard rate is a linear function of time).

This report presents the results of ITC of pembrolizumab monotherapy (KEYNOTE-042) versus pembrolizumab + chemotherapy (KEYNOTE-407) assuming the survival time follows a Log-logistic distribution.

Due to differences in trial protocols between KEYNOTE-042 and KEYNOTE-407 as relates to within-trial cross-over to pembrolizumab, there was an imbalance in the use of immunotherapies among patients receiving a post-discontinuation therapy within the trials. In KEYNOTE-407, there were provisions for protocol-specified within-trial cross-over to pembrolizumab within the chemotherapy arm following disease progression. There was no within-trial cross-over in KEYNOTE-042, and pembrolizumab use in the chemotherapy arm post-discontinuation occurred outside the trial. Thus, use of pembrolizumab post-discontinuation was much lower in KEYNOTE-042 than in KEYNOTE-407.

Analyses were therefore adjusted for switching use a 2-stage approach, which removes the impact of post-discontinuation immunotherapy use within the efficacy estimates from both trials and provides comparability for the chemotherapy arms along this dimension.

The results for the ITC adjusted using the 2-stage approach form the base case of the economic analysis and are presented below in addition to the unadjusted overall survival analyses.

Overview

To estimate the treatment difference of pembrolizumab as monotherapy vs. pembrolizumab in combination with chemotherapy in below listed endpoints, an ITC was conducted based on data from KEYNOTE-407 and KEYNOTE-042:

- OS
- PFS

Sensitivity analyses:

Overall survival adjusted for switch-over of control arm subjects to pembrolizumab 200 mg Q3W or other anti-PD1/PD-L1 therapies was carried out using a simplified two-stage survival analysis model.

Data from KEYNOTE-407 and KEYNOTE-042 is used in this ITC. The ITT population from both trials is used for the analysis of OS and PFS. All randomized subjects are included in the analyses according to the treatment group they were randomized to.

In order to have a common control arm that can serve as anchor in the ITC, patients pre-assigned to Paclitaxel and Carboplatin chemotherapy from KEYNOTE-042 and KEYNOTE-407 and to Nab-Paclitaxel and Carboplatin chemotherapy from KEYNOTE-407 are selected.

Treatment arms and population selection are summarized in Table 21.

Table 21. Population Selection

Trial	Treatment Arms	Population Selection	Database Cutoff Date
KEYNOTE-407	- Pembrolizumab + Chemotherapy[a] - Chemotherapy[a]	Strong PD-L1 subjects (TPS ≥50%)	May 09, 2019
KEYNOTE-042	- Pembrolizumab - Chemotherapy[a]	Squamous histology subjects[b] Strong PD-L1 subjects (TPS ≥50%)	September 04, 2018
a: Paclitaxel and Carboplatin for P042 and P407 and Nab-paclitaxel and Carboplatin for P407 b: P407 only contains squamous subjects, so only those patients are selected from P042.			

This analysis of the ITC has the same inclusion and exclusion criteria as the analysis presented at the point of CDF entry that was based on data from KEYNOTE-042 IA2 and KEYNOTE-407 IA2 analyses.

A total of [redacted] subjects with squamous histology and strong PD-L1 (TPS ≥50%) who were pre-assigned to carboplatin + paclitaxel/nab-paclitaxel were selected in the study KEYNOTE-407, resulting in [redacted] subjects in the pembrolizumab + chemotherapy arm and [redacted] subjects in the chemotherapy arm.

A total of [redacted] subjects with squamous histology and strong PD-L1 who were pre-assigned to carboplatin/paclitaxel were selected from study KEYNOTE-042, including [redacted] subjects in the pembrolizumab monotherapy arm and [redacted] subjects in the chemotherapy arm.

The time-dependent hazard ratios after month 24 are based on small number of patients, resulting in unstable estimates after month 24. Therefore, the time-dependent hazard-ratios are not interpreted after month 24.

Methods

To compare the efficacy of pembrolizumab monotherapy and pembrolizumab + chemotherapy, an indirect treatment comparison was performed based on relevant data from KEYNOTE-407 and KEYNOTE-042. The chemotherapy control arm of the studies was used as anchor point.

The relative treatment effect was measured by the time-dependent Hazard Ratio (HR) and present a non-monotonic behaviour with survival time following the Log-Logistic distribution.

The ITC was performed using the Bucher method.

The traditional ITC based on Bucher et al. uses individual study results (estimated treatment effect and its standard error) to perform indirect comparison of pembrolizumab monotherapy (KEYNOTE-042) versus pembrolizumab combination (KEYNOTE-407) using the common control arm as an anchor.

The methodology can be summarized in two steps:

- The analysis of each individual trial resulting in estimates of the treatment effect (log HR) and its standard error at each of the following timepoints of interest 1,3,6, 9, 12, 15, 18, 21 and 24 months. The bi-dimensional vector consisting of the scale (α) and the shape (λ) characterizing the hazard function and its matrix of covariance were estimated for each treatment arm in each study.

- The indirect treatment comparison using Bucher method

Overall Survival

Parametric model specifications

Arm level

It is considered that the survival time follows a log-logistic distribution; the hazard is a non-linear function of the time, formally:

$$h(t) = \frac{\alpha l t^{\alpha-1}}{1 + l t^{\alpha}}$$

Thus, the scale (α) and the shape (λ) were first estimated for the log-logistic distribution using the general results of asymptotic normality of Maximum Likelihood Estimation (MLE) as well as its covariance matrix. Then the log(hazard) and the standard error were calculated based on these parameter estimates at each of the following timepoints of interest 1,3,6, 9, 12, 15, 18, 21 and 24 months.

Treatment effect (relative effect)

At each timepoint, the treatment effect of treatment arm B (e.g. pembrolizumab monotherapy in KEYNOTE-042) vs. treatment arm A (e.g. control in KEYNOTE-042) in each study was presented as follows:

$$TE_{B\text{-}A} = \log(\text{hazard}_B) - \log(\text{hazard}_A)$$

with $TE_{B\text{-}A}$ being the treatment effect of treatment B vs treatment A.
The standard error (SE) of $TE_{B\text{-}A}$ is calculated using the regular variance formula for 2 additive normal distributions, i.e. by taking the square root of the sum of the variances:

$$SE_{B\text{-}A} = \sqrt{(SE_B)^2 + (SE_A)^2}$$

The 95%CI is then calculated as follows:

$$[95\%CI] = TE_{B-A} \pm 1.96 \cdot \sqrt{(SE_{B-A})}$$

The treatment effect (TE_{B-A}) and it's 95% CI are exponentiated again to calculate the hazard ratio and its 95%CI.

The analysis of progression-free survival was performed using similar methodology as described above for overall survival.

Sensitivity Analyses for Overall Survival

As described above, since subjects in the chemotherapy (control) arm may have received pembrolizumab or anti-PD1/PD-L1 therapies outside of the by protocol-allowed scenario after discontinuation of the protocol treatment, several sensitivity analyses were performed using the 2-stage method. As described above the 2-stage model was chosen which removed the imbalance in the use of immunotherapies among patients receiving a post-discontinuation therapy within the trials.

Overall Survival in the 2-stage model

A two-stage model as described by Latimer et al, was implemented to perform an overall survival analysis adjusting for switchover in the chemotherapy arm in order to balance the use of immunotherapies among patients receiving a post-discontinuation therapy within the trials.

In the 2-stage model, OS is defined similarly as in ITT, but the survival time of the control arm subjects switching to pembrolizumab 200 mg Q3W or anti-PD1/PD-L1 therapies outside of the by protocol-allowed scenario after discontinuation of the protocol treatment is adjusted. Specifically, the survival time after the secondary baseline of control subjects who switched-over to pembrolizumab or anti-PD1/PD-L1 therapies is adjusted multiplicatively by an acceleration factor determined in stage 1, using a regression model applied to post progression survival data.

The analysis presented in this report is the adjustment using 2-stage model without re-censoring for the switch to Pembrolizumab 200 mg Q3W or other anti-PD1/PD-L1 therapies in control arm.

Indirect Treatment Comparison

For each endpoint at each timepoint of interest (1, 3, 6, 9, 12, 15, 18, 21 and 24 months), the Bucher method was applied to derive the ITC treatment effect of pembrolizumab monotherapy (KEYNOTE-042) vs pembrolizumab combination (KEYNOTE-407) (log hazard ratio estimate and its standard error), using the estimated treatment effects (the corresponding log hazard ratio) and its standard errors of the individual trials (KEYNOTE-407, KEYNOTE-042) resulting from the parametric models described in the section above.

Specifically, for any treatment effect at a given timepoint, the Bucher method consisted in the following steps.

The treatment effect (TE) of pembrolizumab monotherapy ('PM') versus pembrolizumab + chemotherapy ('PC') was calculated by using the comparison vs. control ("C") in each trial:

$$TE_{PM\text{-}PC} = TE_{PM\text{-}C} - TE_{PC\text{-}C}$$

with:

- $TE_{PM\text{-}C}$ being the treatment effect of pembrolizumab mono vs control (KEYNOTE-042)
- $TE_{PC\text{-}C}$ being the treatment effect of pembrolizumab combo vs control (KEYNOTE-407)
- $TE_{PM\text{-}PC}$ being the treatment effect of pembrolizumab mono vs pembrolizumab combo by means of the indirect comparison via the control arms.

The standard error (SE) of $TE_{PC\text{-}PM}$ was calculated using the regular variance formula for 2 additive normal distributions, i.e. by taking the square root of the sum of the variances:

$$SE_{PM\text{-}PC} = \sqrt{((SE_{PM\text{-}C})^2 + (SE_{PC\text{-}C})^2)}$$

The 95% CI was then calculated as follows:

$$95\%\ CI = [TE_{PM\text{-}PC} - 1.96 \times SE_{PM\text{-}PC}\ ;\ TE_{PM\text{-}PC} + 1.96 \times SE_{PM\text{-}PC}]$$

The treatment effect ($TE_{PM\text{-}PC}$) and its 95% CI were exponentiated again to calculate the hazard ratio and its 95% CI.

All the endpoints of interest in this report are time to event, the single treatment effect at a given timepoint in each trial was estimated by the log hazard ratio and corresponding standard error. The log hazard ratio was the original estimate from the model; therefore, the results were transformed to hazard ratio by exponentiation.

Results

Overall survival (ITT)

The results of overall survival using the log-logistic distribution by treatment arm for each pairwise comparison (from KEYNOTE-407 and KEYNOTE-042) and for the ITC of pembrolizumab monotherapy vs. pembrolizumab + chemotherapy are provided in the following tables:

- Table 22 for model parameters.
- Table 23 for the overall survival fitted and the corresponding hazard ratios at the timepoints 1, 3, 6, 9, 12, 15, 18, 21 and 24 months. The hazard ratio for the comparison of pembrolizumab monotherapy vs. pembrolizumab + chemotherapy increases over time.

Table 22. Model Parameters of Overall Survival using the Log-Logistic distribution (Intention-to-Treat Population, TPS ≥ 50%)

		Parameters of the model (Log-Logistic)[a]		
		alpha (variance) (95% CI)	**lambda (variance) (95% CI)**	**corr(alpha,lambda) (covariance)**
Study 042[c]	Pembrolizumab Monotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b]	[redacted]	[redacted]	[redacted]
Study 407[d]	Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b]	[redacted]	[redacted]	[redacted]

a: Based on the hazard function following log-logistic distribution
b: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin
c: Database Cutoff Date: 04SEP2018
d: Database Cutoff Date: 09MAY2019
corr: correlation

Source: [16]

Table 23. Analysis of Overall Survival using model based on the Log-Logistic distribution (Intention-to-Treat Population, TPS ≥ 50%)

	Study 042[a]			Study 407[b]			ITC
	Pembrolizumab Monotherapy	Chemotherapy[c]		Pembrolizumab + Chemotherapy	Chemotherapy[c]		
Time point (months)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	HR[e] (95% CI)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	HR[e] (95% CI)	HR[d] (95% CI)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: 04SEP2018

b: Database Cutoff Date: 09MAY2019

c: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin

d: Bucher methodology using separate study results (estimate and its standard error) with a common control arm to perform indirect comparison of effect of monotherapy (P042) vs pembrolizumab combination (P407)

e: Based on the estimates obtained from the hazard function at treatment arm with the hazard function following a log-logistic distribution

Source: [16]

Figure 11 and Figure 12 display the corresponding fitted curves alongside the Kaplan-Meier curves for studies KEYNOTE-407 and KEYNOTE-042, respectively.

Figure 11. Overall Survival (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 407)

Source: [16]

Figure 12. Overall Survival (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 042)

Source: [16]

Overall Survival adjusted for switch-over

Among the [redacted] subjects in the control arm of the study KEYNTOE-042, [redacted] ([redacted] %) switched to other anti-PD1/PD-L1 therapies (including pembrolizumab 200 mg Q3W) outside of the by protocol-allowed scenario after discontinuation of the protocol treatment.

For the study KEYNOTE-407, [redacted] ([redacted]%) subjects among the [redacted] subjects in control arm switched to pembrolizumab 200 mg Q3W or anti-PD1/PD-L1 therapies including both the per protocol and the outside of the by protocol-allowed scenario after discontinuation of the protocol treatment.

Overall Survival in the 2-stage model:

Both direct and indirect switches are considered for the 2-stage adjusted overall survival in the following tables and figures.

The results of the 2-stage adjusted overall survival using the log-logistic distribution by treatment arm for each pairwise comparison (from KEYNOTE-407 and KEYNOTE-042) and for the ITC of pembrolizumab monotherapy vs. pembrolizumab + chemotherapy are provided in the following tables:

- Table 24 for model parameters.
- Table 25 for the overall survival fitted and the corresponding hazard ratios at the timepoints 1, 3, 6, 9, 12, 15, 18, 21 and 24 months. The hazard ratio for the comparison of pembrolizumab monotherapy vs. pembrolizumab + chemotherapy increases over time.

Table 24. Model Parameters of Overall Survival using the Log-Logistic distribution (Intention-to-Treat Population, TPS ≥ 50%) Adjusting for Treatment Switch to Pembrolizumab 200 mg Q3W or Other Anti-PD1/PD-L1 Therapies in Control Arm Using 2-Stage Analysis Without Recensoring

		Parameters of the model (Log-Logistic)[a]		
		alpha (variance) (95% CI)	**lambda (variance) (95% CI)**	**corr(alpha,lambda) (covariance)**
Study 042[c]	Pembrolizumab Monotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b]	[redacted]	[redacted]	[redacted]
Study 407[d]	Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b]	[redacted]	[redacted]	[redacted]

a: Based on the hazard function following log-logistic distribution
b: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin
c: Database Cutoff Date: 04SEP2018
d: Database Cutoff Date: 09MAY2019
corr: correlation

Source: [16]

Table 25. Analysis of Overall Survival using model based on the Log-Logistic distribution (Intention-to-Treat Population, TPS ≥ 50%) Adjusting for Treatment Switch to Pembrolizumab 200 mg Q3W or Other Anti-PD1/PD-L1 Therapies in Control Arm Using 2-Stage Analysis Without Recensoring

	Study 042[a]			Study 407[b]			ITC
	Pembrolizumab Monotherapy	Chemotherapy[c]		Pembrolizumab + Chemotherapy	Chemotherapy[c]		
Time point (months)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	HR[e] (95% CI)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	HR[e] (95% CI)	HR[d] (95% CI)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: 04SEP2018

b: Database Cutoff Date: 09MAY2019

c: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin

d: Bucher methodology using separate study results (estimate and its standard error) with a common control arm to perform indirect comparison of effect of monotherapy (P042) vs pembrolizumab combination (P407)

e: Based on the estimates obtained from the hazard function at treatment arm with the hazard function following a log-logistic distribution

Source: [16]

Figure 13 and Figure 14 display the corresponding fitted curves alongside the Kaplan-Meier curves for studies KEYNOTE-407 and KEYNOTE-042, respectively.

Figure 13. Overall Survival Adjusted for Treatment Switch to Pembrolizumab 200 mg Q3W or Other Anti-PD1/PD-L1 Therapies in Control Arm Using 2-Stage Analysis Without Recensoring (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 407)

Source: [16]

Figure 14. Overall Survival Adjusted for Treatment Switch to Pembrolizumab 200 mg Q3W or Other Anti-PD1/PD-L1 Therapies in Control Arm Using 2-Stage Analysis Without Recensoring (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 042)

Source: [16]

Progression Free Survival

The results of progression-free survival using the log-logistic distribution by treatment arm for each pairwise comparison (from KEYNOTE-407 and KEYNOTE-042) and for the ITC of pembrolizumab monotherapy vs. pembrolizumab + chemotherapy are provided in the following tables:

- Table 26 for model parameters.
- Table 27 for the overall survival fitted and the corresponding hazard ratios at the timepoints 1, 3, 6, 9, 12, 15, 18, 21 and 24 months. The hazard ratio for the comparison of pembrolizumab monotherapy vs. pembrolizumab + chemotherapy increases over time.

Table 26. Model Parameters of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) using the Log-Logistic distribution (Intention-to-Treat Population, TPS ≥ 50%)

		Parameters of the model (Log-Logistic)[a]		
		alpha (variance) (95% CI)	**lambda (variance) (95% CI)**	**corr(alpha,lambda) (covariance)**
Study 042[c]	Pembrolizumab Monotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b]	[redacted]	[redacted]	[redacted]
Study 407[d]	Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b]	[redacted]	[redacted]	[redacted]

a: Based on the hazard function following log-logistic distribution
b: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin
c: Database Cutoff Date: 04SEP2018
d: Database Cutoff Date: 09MAY2019
corr: correlation

Source: [16]

Table 27. Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) using model based on the Log-Logistic distribution (Intention-to-Treat Population, TPS ≥ 50%)

	Study 042[a]			Study 407[b]			ITC
	Pembrolizumab Monotherapy	Chemotherapy[c]		Pembrolizumab + Chemotherapy	Chemotherapy[c]		
Time point (months)	Progression-Free Survival[e] in % (95% CI)	Progression-Free Survival[e] in % (95% CI)	HR[e] (95% CI)	Progression-Free Survival[e] in % (95% CI)	Progression-Free Survival[e] in % (95% CI)	HR[e] (95% CI)	HR[d] (95% CI)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: 04SEP2018

b: Database Cutoff Date: 09MAY2019

c: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin

d: Bucher methodology using separate study results (estimate and its standard error) with a common control arm to perform indirect comparison of effect of monotherapy (P042) vs pembrolizumab combination (P407)

e: Based on the estimates obtained from the hazard function at treatment arm with the hazard function following a log-logistic distribution

Source: [16]

Figure 15 and Figure 16 display the corresponding fitted curves alongside the Kaplan-Meier curves for studies KEYNOTE-407 and KEYNOTE-042, respectively.

Figure 15. Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 407)

Source: [16]

Figure 16. Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 042)

Source: [16]

Conclusion

When the PH assumption is relaxed in order to see the time course of treatment effect, the results show that the hazard ratio for the comparison of pembrolizumab monotherapy vs. pembrolizumab + chemotherapy decreases over time for both OS and PFS (numerical benefit for combination therapy over monotherapy at earlier timepoints to no difference at later timepoints).

A.8 Incorporating collected data into the model

As per the DCA document[8]. clinical data on OS were collected at the FA of KEYNOTE-407 trial for the comparison of pembrolizumab combination versus the trial comparator in the ITT population and across PD-L1 subgroups (as per email communication with NICE on 20th January 2020, 3 sub-groups of patients with PD-L1 expression of ≥ 50%, 1-49% and < 1% are presented). As per the DCA document [8], clinical data on OS were collected at the FA of KEYNOTE-407 trial, for the comparison of pembrolizumab combination versus the trial comparator in the ITT population and across PD-L1 subgroups (as per email communication with NICE on 20th January 2020, 3 sub-groups of patients with PD-L1 expression of TPS ≥ 50%, TPS 1-49% and TPS < 1% are presented). Additionally, clinical data on PFS, ToT and the proportions of patients who received subsequent treatments as well as the duration of these treatments were also collected from the FA and were incorporated into the economic model.. For the PD-L1 subgroup with TPS ≥50%, the ITC of pembrolizumab combination versus pembrolizumab monotherapy was updated to incorporate the data collected from the FA of KEYNOTE-407 for this subgroup (see A.7.1).

Guidance from the NICE DSU TSD14 was followed to identify base case parametric survival models for OS and PFS, and ToT.

A.8.1 *Overall survival*

As per the NICE DSU TSD 14 document, first, the PH assumption was tested to assess whether joint or separate statistical models were more appropriate for the pembrolizumab and SOC treatment arms:

```
                        rho chisq     p
TRT01PPembro Combo 0.0624   1.4 0.236
```

According to the test result, there is not enough statistical evidence against “the proportional hazard ratio” assumption. And by checking the residual plot below, it might be fine to assume proportion hazard ratio.

Figure 17. Schoenfeld Residual Plot for Pembrolizumab Combination

However, upon visual inspection of the cumulative hazard and the log cumulative hazard plots, the curves do not appear to be parallel as they come very close in the beginning of the plots. Therefore, individual model fitting for each treatment arm was undertaken.

Figure 18. Cumulative hazard plot for pembrolizumab combination and control arm - OS

Figure 19. Log Cumulative hazard plot for pembrolizumab combination and control arm - OS

In addition to the plots above, Chow tests (

Figure 20, Figure 21) were examined to identify any potential structural change in the cumulative hazard. It is acknowledged that from the plots, the rate can be considered broadly constant however for the pembrolizumab combination arm, a slight change in the hazard can be seen in week 23 while for the SoC arm this is observed at week 35. Therefore, as a base case a fully fitted curve (no cut off point) was selected but these two cut-off points were considered as scenario analyses.

Figure 20. Chow test plot for OS for SoC

Figure 21. Chow test for OS for pembrolizumab combination

All standard parametric curves were fitted to OS KM data for both arms.

Figure 22. OS KM curve vs fitted parametric curves (no cut-off point) for pembrolizumab combination arm

Figure 23. OS KM curve vs fitted parametric curves (no cut-off point) for SoC arm

Within the various parametric survival models explored, visual inspection was used to assess the fit of the curves to the observed clinical trial data. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) statistics were also calculated for both arms to assess goodness-of-fit and parsimony.

Table 28. AIC and BIC statistics for piecewise parametric model for OS

Fitted Function	Pembrolizumab + Chemotherapy		Chemotherapy	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
GenGamma	[redacted]	[redacted]	[redacted]	[redacted]

For pembrolizumab combination, the exponential function had the lower BIC statistic while Weibull had the lowest AIC. For chemotherapy arm, LogLogistic had the lowest AIC while exponential had the lowest BIC, followed closely by LogLogistic.

LogLogistic was preferred in terms of the statistical fit because it had on average the lowest difference from the best AIC and BIC in each arm (PC: ΔAIC~ 1.1, ΔBIC~1.2, SoC: ΔAIC~0, ΔBIC~0.7).

Figure 24. OS Parametric Function Fittings Based on the Log-Logistic Distribution for Each Trial Arm

Apart from consistency with the committee preferred extrapolation curve in the original submission, the LogLogistic extrapolation provided the most clinically plausible 5-year and 10-year OS compared to exponential and Weibull.

Table 29. 5-year and 10-year OS for pembrolizumab combination and chemotherapy arm for each fully fitted parametric extrapolation curve

	Pembrolizumab combination		Chemotherapy	
	5-year OS	10-year OS	5-year OS	10-year OS
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
GenGamma	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 29, LogLogistic extrapolation provided estimates that are closer to clinical opinion elicited from ERG and MSD in the original submission (ERG report p.126). Additionally, the committee's accepted OS extrapolated LogLogistic curve in the original submission resulted in the following estimates:

Table 30. 5, 10 and 20 – year OS estimates for pembrolizumab combination and chemotherapy arm based on ERG's pessimistic scenario from the original submission (ERG's log logistic model [no cut-point])

	5-year OS	10-year OS	20-year OS
Pembrolizumab combination	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]

A.8.2 *Progression Free Survival*

In KEYNOTE-407, the first radiologic tumour response assessment was performed at week 6. This resulted in a protocol-driven drop in PFS by BICR between weeks 5 and 7, impacting the ability to adequately fit a single parametric curve to PFS data, so to be able to extrapolate beyond the clinical trial period. Further evaluation of the data was conducted according to the NICE DSU guidance:

The PH assumption was tested. There was not enough statistical evidence against "the proportion hazard ratio" assumption:

```
                        rho chisq     p
TRT01PPembro Combo 0.0206 0.197 0.657
```

However, upon visual examination of the cumulative hazard plot (**Error! Reference source not found.**) it was evident that the PH assumption was violated since the two treatment groups seem to cross towards the beginning and the lines are not parallel.

Figure 25. Cumulative hazard plot for pembrolizumab combination and control arm - PFS

Inspection of output from Chow tests and cumulative hazard function suggests that there are further substantive changes in the slope in the PFS hazard function beyond week 6 with the most notable change on week 26 for both arms.

Figure 26. Chow test plot of PFS (BICR) for pembrolizumab + chemotherapy

Figure 27. Chow test plot of PFS (BICR) for chemotherapy

All standard parametric curves were fitted to PFS data after week 26 both for pembrolizumab combination and for the SoC arm separately.

Figure 28. PFS KM curve vs fitted piecewise model with cut-off at 26 weeks for pembrolizumab combination arm

Figure 29. PFS KM curve vs fitted piecewise model with cut-off at 26 weeks for SoC arm

Within the various parametric survival models explored, visual inspection was used to assess the fit of the curves to the observed clinical trial data. The Akaike Information Criterion (AIC) and the

Bayesian Information Criterion (BIC) statistics were also calculated for both arms to assess goodness-of-fit and parsimony.

Table 31. AIC and BIC statistics for piecewise parametric model for PFS week 26

Fitted Function	Pembrolizumab + Chemotherapy		Chemotherapy	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
GenGamma	[redacted]	[redacted]	[redacted]	[redacted]

According to the AIC and BIC values, the LogNormal parametric function provides the best fit for PFS extrapolation for both trial arms. This distribution is chosen as the model base case distribution.

Figure 30. PFS KM Data Followed by Parametric Curve Fitting from 26 Weeks Onwards in the Pembrolizumab + Chemotherapy Arm Based on the LogNormal Distribution

Figure 31. PFS KM Data Followed by Parametric Curve Fitting from 26 Weeks Onwards in the Chemotherapy Arm Based on the LogNormal Distribution

Figure 32. Modelled PFS functions for pembrolizumab combination and trial chemotherapy arm included in base case analysis, week 26 cut-point

A.8.3 *Time on treatment*

In KEYNOTE-407, patients in both trial arms could discontinue treatment at any time due to adverse events, disease progression, inter-current illness, protocol non-compliance or investigator or patient preference. In the case of disease progression, patients could continue on pembrolizumab treatment post-progression if, in the investigator's opinion, the patient was deriving benefit from treatment. Thus, rather than assuming that treatment terminated with disease progression, so as to capture actual resource utilization associated with observed clinical outcomes in the trial, patient data corresponding to actual ToT were analyzed to better capture treatment costs.

Consistently with the original submission, for the SoC arm, as a maximum of 4 cycles of treatment is specified within the trial, well within the available trial follow-up time, KM data for the ToT in the chemotherapy arm are used directly within the model. For the pembrolizumab combination therapy, standard parametric models were fitted to the observed KM data from KEYNOTE-407 FA (maximum follow up [redacted] weeks) (Figure 33).

Figure 33. Modelled ToT functions, pembrolizumab combination arm in KEYNOTE-407 FA

Upon visual inspection, the AIC and BIC statistics were also examined (Table 32).

Table 32. AIC and BIC statistics for parametric curve-fitting for ToT within the overall population of KEYNOTE-407

Fitted Function	Pembrolizumab + Chemotherapy		Chemotherapy	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	n/a	n/a
Weibull	[redacted]	[redacted]	n/a	n/a
LogNormal	[redacted]	[redacted]	n/a	n/a
LogLogistic	[redacted]	[redacted]	n/a	n/a
Gompertz	[redacted]	[redacted]	n/a	n/a
GenGamma	[redacted]	[redacted]	n/a	n/a

The GenGamma curve had the lower AIC statistic while the exponential had the lower BIC statistic. Since the BIC for GenGamma was closer to the lower BIC (ΔBIC – 0.9) than the Exponential AIC to the lower AIC (ΔBIC - 6.4) the GenGamma was selected for the ToT extrapolation.

Figure 34. Modelled ToT functions for all treatment options included in the base case analysis

Additionally, a different ToT was also tested on a scenario analysis. As no patients were still on pembrolizumab + chemotherapy treatment among those with the longest available follow-up times, time on treatment was also directly estimated from KM data in the scenario analyses.

A.8.4 *Subsequent therapies*

% of patients discontinuing treatment that utilize a post-discontinuation therapy

The percentage of patients who received subsequent lines of therapy after treatment discontinuation (37.4% for pembrolizumab + chemotherapy and 60.7% for chemotherapy) was estimated from the KEYNOTE-407 FA. Analogously, the proportion of pembrolizumab monotherapy patients with squamous histology (n = 29) that discontinued treatment and went on to receive a subsequent therapy was 31.0% within KEYNOTE-024.

Distribution of second-line active treatments

The actual distribution of specific treatments post-discontinuation from the KEYNOTE-407 FA was presented in Table 19. However, the distribution modelled in the cost effectiveness analysis was different (Table 33). For the chemotherapy arm, patients may receive in the 2nd line pembrolizumab monotherapy or atezolizumab (25% vs 75% respectively) as per the committee's preference in the FAD. For the chemotherapy arm and pembrolizumab monotherapy arm, only 2nd line treatments used by at least 5% of patients receiving 2nd line of therapy are explicitly modelled. The percentages of patients receiving any other specific treatment are redistributed among the remaining most frequently used treatments to ensure that the total proportion receiving subsequent therapy in each arm is aligned with the trial data. Nivolumab was not included in the 2nd line therapies in the model because it is in the CDF. Additionally, nab-paclitaxel was also excluded as it is not commissioned in the UK.

While the costs of subsequent therapies are separately included in the model, OS and PFS impacts are assumed to be already reflected within the OS and PFS Kaplan-Meier data from the KEYNOTE-407 trial, without switching adjustment.

Table 33. Distribution of second-line+ active treatments modelled

Post-discontinuation regimen (dose)	Pembrolizumab + Chemotherapy Arm	Chemotherapy Arm	Pembrolizumab Monotherapy
Patients who received anti-PD1/PD-L1 therapy only			
Atezolizumab		75.0%	
Pembrolizumab (200 mg)		25.0%	
Patients who received chemotherapy only			
Carboplatin (400 mg/m^2) + Gemcitabine (1250 mg/m^2)	[redacted]	[redacted]	[redacted]
Carboplatin (400 mg/m^2) + Paclitaxel (200 mg/m^2)	[redacted]	[redacted]	[redacted]
Cisplatin (75 mg/m^2) + Gemcitabine (75 mg/m^2)	[redacted]	[redacted]	[redacted]
Cisplatin (75 mg/m^2) + Paclitaxel (200 mg/m^2)	[redacted]	[redacted]	[redacted]
Docetaxel (75 mg/m^2)	[redacted]	[redacted]	[redacted]
Gemcitabine (1250 mg/m^2)	[redacted]	[redacted]	[redacted]

Average treatment duration in weeks for subsequent 2nd-line active treatment

The modelled number of weeks of use of additional therapies following discontinuation of initial treatment (either pembrolizumab + chemotherapy, chemotherapy or pembrolizumab monotherapy) for the overall trial population analysis is shown in Table 34. Durations reflect the number of weeks of subsequent use within a line of therapy within a given category of post-discontinuation regimen (e.g., chemotherapies).

For post-discontinuation chemotherapy use, where treatment durations tend to be relatively short and therapies generally inexpensive, treatment durations reflect values observed within the KEYNOTE-407 FA data. For post-discontinuation anti-PD1/PD-L1 therapy use, treatment durations tend to be much longer. Given right censoring observed within the KEYNOTE-407 FA data for the durations of these treatments in 2L, limiting the observation window and under-estimating mean durations for these regimens, it was elected to instead use in the base case estimates of mean duration for these therapies based on TA520 for atezolizumab[17]and from KEYNOTE-010 (Data-cut March 2018) for pembrolizumab[18]. As per TA520: "*Based on the OAK trial, the average time on therapy per patient (mean) is 7.78 months, equivalent to 11.3 cycles* ". Therefore, for modelling purposes it was assumed a mean of 33.9 weeks of atezolizumab treatment in 2L. Similarly, based on KEYNOTE-010, the mean number of administrations was 10.3 therefore an average treatment duration of 30.9 weeks was assumed for pembrolizumab in 2L (Table 34).

The duration of chemotherapy use post-discontinuation was estimated for pembrolizumab monotherapy from KEYNOTE-024 for 2nd line therapy use.

Table 34. Duration in days of 2nd line treatment regimens modelled

Post-discontinuation regimen	Pembrolizumab + Chemotherapy	Chemotherapy Arm	Pembrolizumab Monotherapy
Patients who received anti-PD1/PD-L1 therapy -atezolizumab		[redacted]	
Patients who received anti-PD1/PD-L1 therapy -pembrolizumab		[redacted]	
Patients who received chemotherapy only	[redacted]		[redacted]

A.9 Key model assumptions and inputs

Table 35 Key model assumptions and inputs

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
OS data extrapolation Company submission section B.3.3.1 and Appendix L 'Modelling overall survival (original submission)	A LogLogistic model with no cut point for both treatment arms was considered from the committee more appropriate for decision making for the overall population.	Consistently with the original submission, a LogLogistic model with no cut point for both treatment arms is applied in the base case.	Goodness of fit statistics, visual inspection and clinical plausibility suggest that the LogLogistic is the best fitting extrapolation for the updated clinical data.
PFS Company submission section B.3.3.1 and Appendix L 'Modelling progression free survival (original submission)	PFS was modelled using a piece-wise log-normal curve using a 26-week cut-point of observed KM data in each treatment group	Consistently with the original submission, PFS was modelled using a piece-wise log-normal curve using a 26-week cut-point of observed KM data in each treatment group	Goodness of fit statistics and visual inspection suggests that the log-normal is the best fitting extrapolation for the updated PFS clinical data. Additionally, 5-year PFS estimates were consistent with clinical expert opinion elicited from the ERG in the original submission (5-year PFS probabilities for the pembrolizumab combination therapy and the SoC chemotherapy groups of 0.10 and 0.03, respectively)
ToT B.3.5.2 (original submission)]	ToT was modelled using a non-piecewise GenGamma curve. Maximum treatment duration of 2 years assumed in the pembrolizumab combination arm, while maximum treatment duration of 12 weeks used in the SoC arm.	Consistently with the original submission, ToT was modelled using a non-piecewise GenGamma curve. Maximum treatment duration of 2 years assumed in the pembrolizumab combination arm, while maximum treatment duration of 12 weeks used in the SoC arm.	Goodness of fit statistics and visual inspection suggests GenGamma was the best fitting extrapolation for the updated ToT clinical data.

Duration of treatment benefit B.3.2.2 Table 56	The committee considered the lifetime treatment effect of pembrolizumab combination to be implausible and considered that a treatment effect lasting between 3 to 5 years is more appropriate.	Based on committee's preference, a 5-year treatment duration benefit was applied in the base case. Scenarios for 3 and 4 years were also implemented	While no evidence exists to support that treatment benefit of pembrolizumab will wane after 5 years, for consistency with previous immunoncology therapies, a 5-year treatment benefit duration was applied.
Utilities Company submission B.3.4.5	The committee preferred to use progression-based utilities with a pre-progression utility from KEYNOTE-407 and a post-progression utility from TOPICAL (Khan et al. 2014)	Consistently with committee's preference, progression-based utilities with a pre-progression utility from KEYNOTE-407 and a post-progression utility from TOPICAL (Khan et al. 2014) was implemented.	MSD considers the utility values reported in the Khan paper too low as the population in the TOPICAL trials had several comorbidities and significantly worst ECOG status compared to the population of this indication. A scenario with post-progression utilities from KEYNOTE-407 was also applied.
Subsequent therapies	The committee preferred the assumption that around 50% of people in the SoC arm will be offered subsequent treatments out of which 75% would have atezolizumab and 25% pembrolizumab in NHS clinical practice.	Consistently with committee's preference, patients in the SoC were assumed to receive 25% pembrolizumab and 75% atezolizumab in the 2L. While data was collected from KEYNOTE-407 FA for the duration of treatment in 2L, the base case of the duration of the 2L treatments was based on the pivotal trials for pembrolizumab and atezolizumab in 2L. The proportion of patients who discontinue treatment and utilize a post-discontinuation therapy was also updated for KEYNOTE-407 data.	Given right censoring observed within the KEYNOTE-407 FA data for the durations of these treatments in 2L, limiting the observation window and under-estimating mean durations for these regimens, it was elected to instead use estimates of mean duration for these therapies based on the pivotal trials for pembrolizumab and atezolizumab in 2L. See further information in section A.8.4

A.10 Cost-effectiveness results (deterministic)

[Present the results from the economic model submitted for the CDF review for the following cost-effectiveness analyses:
(1) Replication of the key cost-effectiveness result(s) considered by committee to demonstrate plausible potential for cost-effectiveness at entry to the CDF;
(2) Cost-effectiveness results that incorporate the data collected during the CDF data collection

period, with all model inputs and parameters unchanged from cost-effectiveness analysis (1).
(3) Cost-effectiveness results that incorporate data collected during the CDF data collection period plus any associated changes to the company's preferred assumptions]
Note: when multiple data sources and/or assumptions are altered following the CDF data collection period, please provide scenario analyses which illustrate the impact of each individual change in the appendix.

(Please note: MSD used the economic model provided by NICE named: 'ERG expl 6b- pessimistic ERG preferred model paclitaxel Atezolistprice 23April2019 [ACiC]' to update with the FA data collected during the CDF data collection period. Data from IA2 of KEYNOTE-407 were also retained in the same model provided by NICE, so that NICE can replicate the results from the original submission within the same model and confirm that no structural changes were conducted. However, when the settings in MSD's updated model are set exactly as per the ERG preferences for the IA2 data, the results do not match those from the ERG version received from NICE:

Results for IA2 – ERG preferences from MSD's updated model are presented in Table 36 Cost effectiveness analysis 1.

Results for IA2 – ERG preferences from ERG model are presented in Table 36 cost effectiveness analysis 2.

Upon further investigation, MSD identified that in the ERG model received from NICE, in the tab 'Modeled OS', cells V and W, hard values were pasted (rather than formulas) and MSD were not able to replicate the exact hard values as no 'precedent links' existed for these two columns. Looking at the ERG report page 175, MSD identified that the ERG pasted these values from another file named 'ERG curve fitting – KEYNOTE-407' which MSD didn't have

access to. However, in order to validate the consistency in the structure between MSD's updated model and the ERG model, MSD tested the values from the ERG model (tab 'Modeled OS', cells V and W) to the respective tab in MSD's updated model. Then, results matched the preferred ICER of the ERG. [redacted]).

Table 36 Cost-effectiveness results (deterministic)

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental. costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER versus baseline (£/QALY)**	**Incremental ICER (£/QALY)**
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – ***MSD's updated model***								
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,851	£44,851
Cost-effectiveness analysis 2: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – **original ERG model named: 'ERG expl 6b- pessimistic ERG preferred model paclitaxel Atezolistprice 23April2019 [ACiC]'**								
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,224	£43,224
Cost-effectiveness analysis 3: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence								
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,734	£56,734
Cost-effectiveness analysis 4: New company base-case								
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,090	£38,090

A.11 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The incremental cost-effectiveness results obtained from the PSA are presented in. The results show that the PSA results are very similar to the deterministic results.

Table 37 Updated base-case results (probabilistic)

	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Trial chemotherapy arm	[redacted]	[redacted]			
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£38,834

The corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 35 and Figure 36. The cost-effectiveness acceptability curve shows that there is approximately a 68.5% probability of pembrolizumab combination being cost-effective when compared to trial chemotherapy arm at the £50,000 per QALY threshold applicable to end-of-life technologies.

Figure 35 Scatterplot of probabilistic results

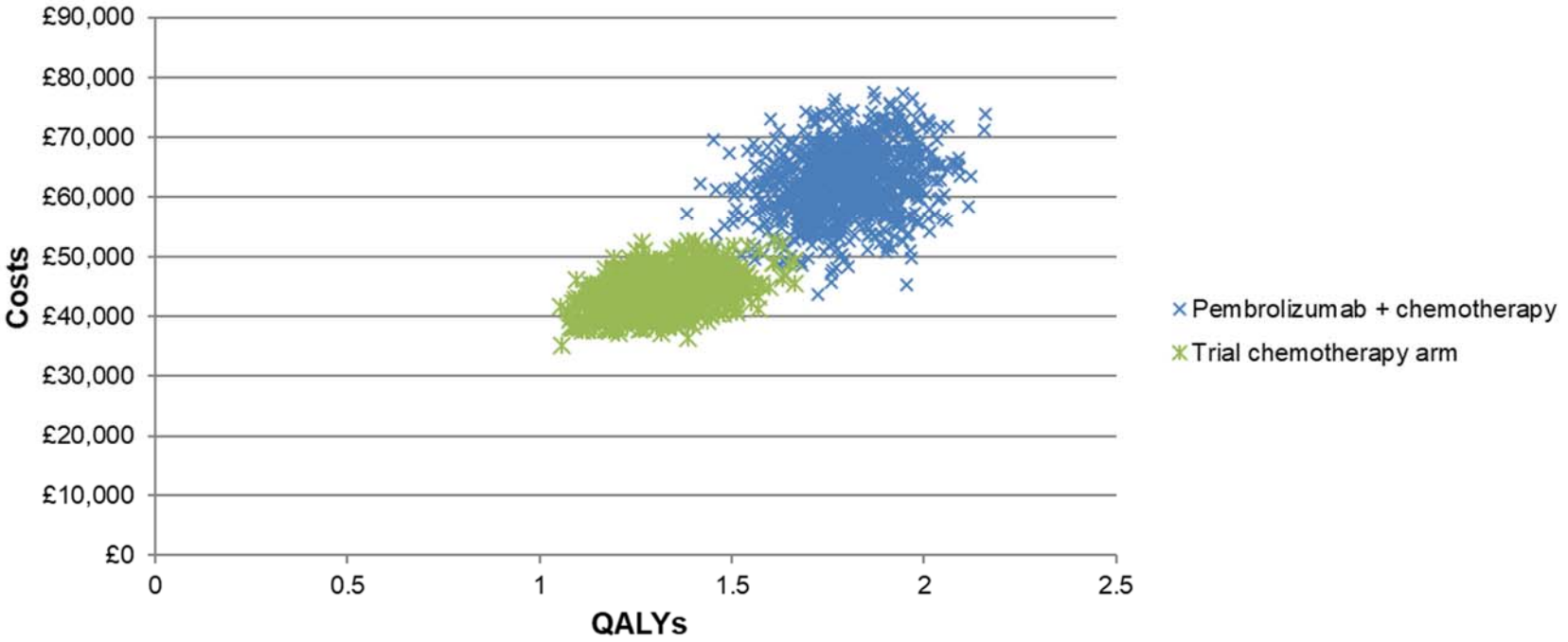
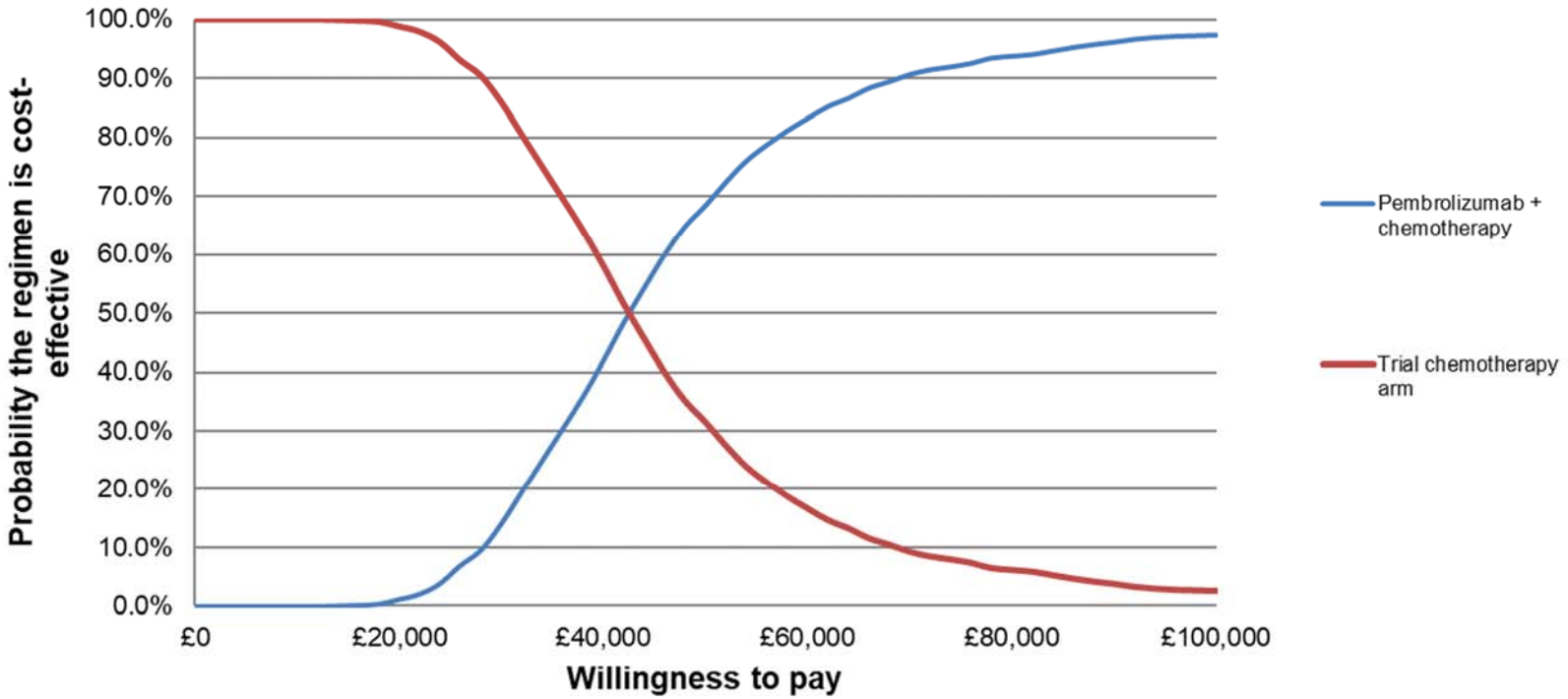


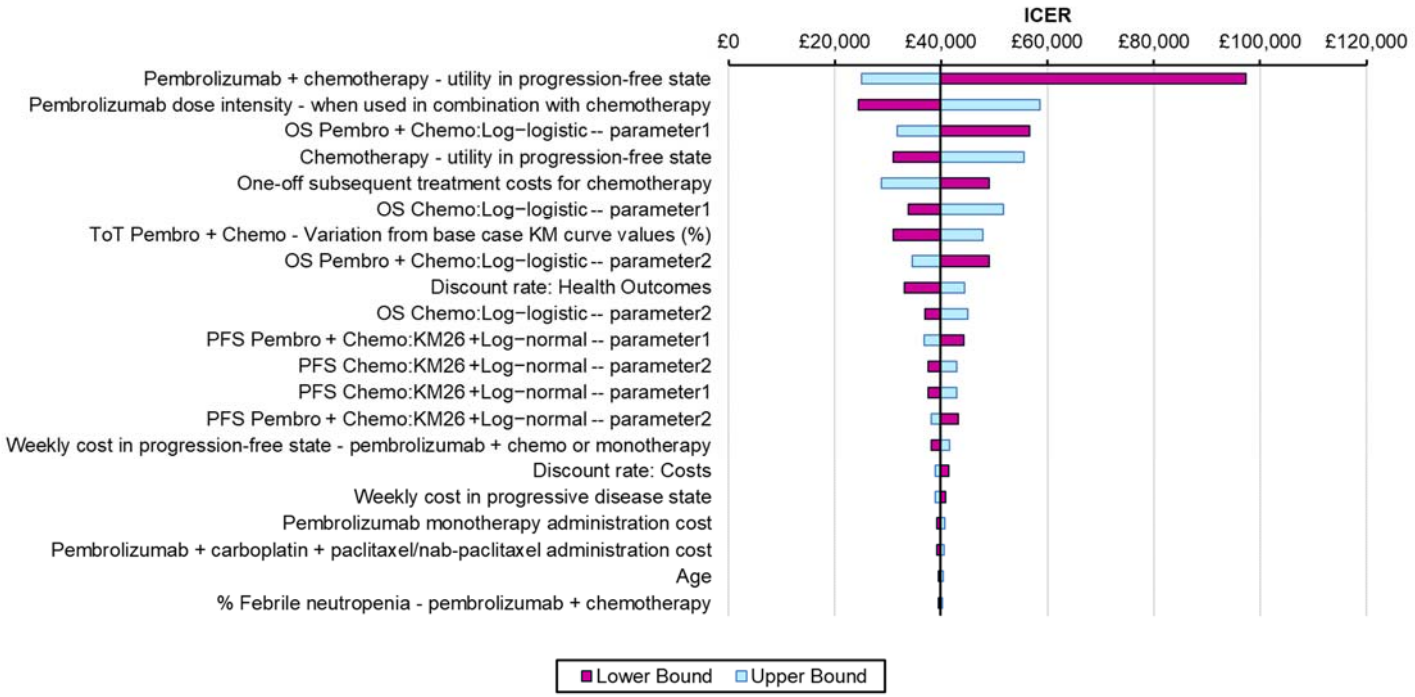
Figure 36 Cost-effectiveness acceptability curve (results discounted, with PAS)



A.12 Key sensitivity and scenario analyses

The tornado diagram depicted in Figure 37 shows the impact of parameter variation on the ICER as derived from the one-way sensitivity analysis (OWSA) for pembrolizumab versus UK SoC. The variations that had the most impact on the ICER were the progression-free utilities for the pembrolizumab combination arm, the dose intensity of pembrolizumab combination and the OS parametric extrapolation for pembrolizumab combination.

Figure 37. Tornado diagram, deterministic sensitivity analysis, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nabpaclitaxel



Detailed results of the OWSA are presented in Table 38 the ICER ranged from £4,432.92/QALY to £97,350.89/QALY for pembrolizumab combination versus carboplatin plus paclitaxel/nabpaclitaxel.

Table 38. One-Way Sensitivity Analysis Results

Parameter	Lower bound-ICER	Upper bound-ICER
Pembrolizumab + chemotherapy - utility in progression-free state	£97,350.89	£25,050.12
Pembrolizumab dose intensity - when used in combination with chemotherapy	£24,432.92	£58,589.28
OS Pembro + Chemo:Log−logistic -- parameter1	£56,625.61	£31,785.70
Chemotherapy - utility in progression-free state	£31,033.61	£55,651.55
One-off subsequent treatment costs for chemotherapy	£49,014.46	£28,699.82
OS Chemo:Log−logistic -- parameter1	£33,898.85	£51,693.21
ToT Pembro + Chemo - Variation from base case KM curve values (%)	£30,966.02	£47,804.95
OS Pembro + Chemo:Log−logistic -- parameter2	£49,023.55	£34,513.46
Discount rate: Health Outcomes	£33,107.12	£44,350.73

Table 39 Key scenario analyses

Scenario and cross reference	**Scenario detail**	**Brief rationale**	**Impact on base-case ICER**
Base case			£38,090
In the base case, a fully fitted LogLogistic curve was selected to extrapolate for both arms based on statistical and visual fit as well as clinical plausibility. This is in line with the fully fitted approach implemented by the ERG and accepted by the committee	Alternative OS parametric extrapolation: Fully fitted (week 0) lognormal	Alternative parametric extrapolation: The lognormal was tested in a scenario analysis and while provided worst statistical fit provides clinically plausible outcomes. (5-year OS 17% for pembrolizumab combination and 11% for chemotherapy arm)	£38,024 [-£66]

In the base case, a fully fitted LogLogistic curve was selected to extrapolate for both arms based on statistical and visual fit as well as clinical plausibility. This is in line with the fully fitted approach implemented by the ERG and accepted by the committee	Alternative OS extrapolation: Piecewise extrapolation at week 23	In the OS cumulative hazard plot, a slight change in the hazard was observed in week 23. The piecewise method has been previously implemented for extrapolating OS in NSCLC. Therefore, a scenario was tested where KM data were used up to week 23 and then extrapolated for the rest of the time horizon with a LogLogistic extrapolation (2nd best AIC/BIC statistic, clinically plausible 5-year OS: 17% for pembrolizumab combination and 11% for chemotherapy arm)	£37,626 [-£464]
In the base case, a fully fitted LogLogistic curve was selected to extrapolate for both arms based on statistical and visual fit as well as clinical plausibility. This is in line with the fully fitted approach implemented by the ERG and accepted by the committee	Alternative OS extrapolation: Piecewise extrapolation at week 35	In the OS cumulative hazard plot, a slight change in the hazard was observed in week 35. The piecewise method has been previously implemented for extrapolating OS in NSCLC. Therefore, a scenario was tested where KM data were used up to week 35 and then extrapolated for the rest of the time horizon with a LogLogistic extrapolation(5-year OS: 15% for pembrolizumab combination and 12% for chemotherapy arm)	£38,164 [+£74]
Long term treatment effect. As per the FAD: The committee concluded that a treatment effect lasting between 3 and 5years from the start of treatment has been considered more appropriate for those with a 2-year stopping rule. In the base case the treatment was capped at 5 years from the start of treatment.	3-year cap on benefits of pembrolizumab from the start of treatment and a longer 10-year cap on the benefits	3 years chosen as a scenario based on committee accepted assumption of 3 or 5 years. 10 years chosen in view of clinical trial data and clinical expert opinion, which suggests that longer term duration of treatment effect is associated with immunotherapies due to their distinct mechanism of action	£38,833 [+ £743] £38,063 [-£27]
In the base case, ToT was based on parametric extrapolation of the full KM curve.	KM data were directly applied in the ToT for pembrolizumab combination	As no patients were still on pembrolizumab + chemotherapy treatment among those with the longest available follow-up times, ToT could also be directly estimated from KM data	£39,847 [+£1757]

A.13 End-of-life criteria

Table 40 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The median OS for the chemotherapy arm in KEYNOTE-407 was 11.6 months while the modelled OS for chemotherapy arm for the base case was 2.26 (undiscounted) years. However, clinical experts stated during the committee meeting of TA600 that life expectancy for the ITT population is under 24 months even when accounting for the higher life expectancy for people whose tumours express a PD-L1 tumour proportion score of 50% or higher. Also, squamous populations tend to have poorer prognosis that those with a non-squamous NSCLC and since pembrolizumab combination in non-squamous population has been found by NICE to meet the end of life criteria[19], it is clinically logical that squamous population also meets them.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The median OS gain reported in KEYNOTE-407 was 5.5 months (Table 3) while the modelled OS gain was 5.7 months (0.69 undiscounted life years gained). These figures indicate with confidence that the extension to life criterion is met.

A.14 Key issues and conclusions based on the data collected during the CDF review period

The results from the FA of KEYNOTE-407 provide clear evidence that treatment with pembrolizumab combination provides clinically meaningful benefit compared to the SoC, in the ITT and across PD-L1 TPS subgroups (section A.6). The OS and PFS analysis reported from the FA shows that pembrolizumab combination substantially reduces the risk of death by 29% and reduces risk of disease progression or death by 43% compared with the SoC in patients with untreated, metastatic, squamous NSCLC. The results are not only consistent with the previous data-cut presented at the point of CDF entry, but also demonstrates a continued improvement in OS and PFS over the time with pembrolizumab combination when compared to SoC.

The present submission estimates the cost-effectiveness of the addition of pembrolizumab to carboplatin and paclitaxel/nab-paclitaxel chemotherapy in chemotherapy-naive, metastatic, squamous NSCLC in the UK. The cost-effectiveness of pembrolizumab has again been evaluated through a partitioned survival model, which projected health outcomes (i.e. OS and PFS) to estimate patients' HRQoL and costs.

Based on the uncertainties identified at the point of CDF entry, OS, PFS and ToT were collected from the FA and updated in the model. Additionally, the proportions and duration of 2L treatments were also updated, because subsequent therapies were identified as parameters which impact the efficacy and costs of the intervention and the comparator. QALYs were estimated by considering the preferred approach of the committee: utilities derived from EQ-5D data collected in KEYNOTE-407 trial for the progression-free patients and utilities derived from literature for the patients in the progressed state. Clinical and economic outcomes were projected over a 30-year time horizon to cover the anticipated lifetime of the population initiating first line therapy and assessed as part of this submission.

A fully fitted parametric approach was used to extrapolate the data based on KEYNOTE-407 data, following NICE DSU guidance. The addition of pembrolizumab to carboplatin + paclitaxel/nab-paclitaxel chemotherapy is projected to extend patient life expectancy relative to use of chemotherapy alone. For instance, life expectancy is projected to be extended by more than 25% to approaching 2.5 years in the full trial population. In the base case analysis, the addition of pembrolizumab to carboplatin and paclitaxel/nab-paclitaxel within the KEYNOTE-407 trial is estimated to increase patient survival by 0.69 years (0.58 years with discounting), relative to treatment with carboplatin and paclitaxel/nab-paclitaxel alone. It should be noted that this estimate includes treatment switching to PD-1/PD-L1 treatments following discontinuation of initial treatment in a subset of patients within the carboplatin and paclitaxel/nab-paclitaxel trial arm. The ICER when comparing pembrolizumab combination to UK SoC is £38,090 (PAS included). The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per QALY gained is 68.5%. The most influential drivers of the cost-effectiveness ratio are the progression-free utilities for the pembrolizumab combination arm, the dose density of pembrolizumab combination as well as the OS for pembrolizumab combination.

Pembrolizumab in combination for adults with untreated, metastatic, squamous NSCLC meets NICE's criteria to be considered as a life extending treatment at the end of life, as the median OS gain reported in KEYNOTE-407 was 5.5 months while median OS for the chemotherapy arm in KEYNOTE-407 was 11.6 months. Whilst the base case projected a mean OS for chemotherapy arm of 2.26 years, clinical opinion strongly suggests that the average survival of squamous population is less than 24 months.

The results demonstrate that pembrolizumab combination, as an end of life therapy, meets the NICE criteria to be considered a cost-effective use of NHS resources. The ICER is within the threshold of £50,000 per QALY for 'end-of-life' technologies that applies to pembrolizumab combination for the treatment of metastatic, squamous non-small-cell lung cancer.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1683]

Clarification questions

April 2020

File name	Version	Contains confidential information	Date
ID1683 ERG clarification letter Additional Evidence Redacted	V 1.0	Yes	06/04/2020

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

PD-L1 TPS subgroup (Section A.6.2, pages 22-23, Figure 3 and Table 5)

A1. Priority question. The y-axis label for Figure 3 refers to "% remaining in response", whilst the title of the figure refers to OS. In addition, the numbers of patients at risk at randomisation in Figure 3 do not match those presented in Table 5. Please explain these apparent discrepancies and update Figure 3 and/or Table 5, as appropriate.

The answer to this question was submitted in response to the clarification questions on 19th March 2020.

Section B: Clarification on cost-effectiveness data

Treatment switching adjustment (Section A.7.1, pages 47 to 65)

B1. Please clarify whether adjustment of the pembrolizumab arms (for continued pembrolizumab beyond 35 cycles) was considered in either KEYNOTE-407 or KEYNOTE-042.

The answer to this question was submitted in response to the clarification questions on 19th March 2020.

B2. Please confirm that switching to pembrolizumab in the chemotherapy arm could only happen after disease progression in both KEYNOTE-407 and KEYNOTE-042.

The answer to this question was submitted in response to the clarification questions on 19th March 2020.

B3. The simple 2-stage method can be prone to bias if there is a gap between the time of progression and the time of the switch. Please plot time from progression to switch for switchers in both KEYNOTE-407 and KEYNOTE-042.

The answer to this question was submitted in response to the clarification questions on 19th March 2020.

B4. The analyses presented do not include re-censoring and thus may be prone to informative censoring. Please present the results of the analyses with re-censoring.

The overall result of the indirect treatment comparison (ITC) of pembrolizumab monotherapy (KEYNOTE-042) versus pembrolizumab + chemotherapy (KEYNOTE-407) in overall survival adjusted using 2-stage without re-censoring is presented in a seperate report. The outcome presented in this section is mainly for the indirect treatment comparison of pembrolizumab monotherapy versus pembrolizumab + chemotherapy in overall survival adjusted using 2-stage with re-censoring.

It should be noted that for each study, the acceleration factor was derived by an AFT model in the stage 1 of the 2-stage model as described in MSD's response to the clarification questions submitted to NICE 19th March 2020. After adjusting the overall survival time for switched control subjects based on the acceleration factor estimated by an AFT model, the following re-censoring procedure is applied in all chemotherapy control subjects for both trials to maintain the assumption of non-informative censoring. Re-censoring does not affect the survival status or the survival time for subjects from the pembrolizumab arm in KEYNOTE-042 and the pembrolizumab + chemotherapy arm in KEYNOTE-407. However, while re-censoring might be considered to avoid informative censoring, it may be associated with other sources of bias resulting from the potentially important loss of information (lower number of events and shorter follow-up time).

- Re-censoring

Given that the estimated acceleration factor is greater than 1, the earliest possible censoring time is defined as:

C* = (Date of data cutoff – Date of Randomization+1) × (1/Acceleration Factor)

Then for subjects who died, if the (adjusted) survival time is larger than C*, the patient survival status is changed from "event" to "censored" with adjusted survival time equal to C*;

For subjects who are censored, if the (adjusted) censored survival time is larger than C*, the adjusted censored survival time is equal to C*;

An ITC was performed based on overall survival adjusted for treatment switching using 2-Stage model with re-censoring from both trials, to compare the treatment effect of pembrolizumab monotherapy and pembrolizumab + chemotherapy. The chemotherapy control arm of the studies was used as anchor point. The relative treatment effect was measured by the time-dependent Hazard Ratio (HR) and present a non-monotonic behaviour with survival time following the log-logistic distribution in each study. The ITC was then performed using the Bucher method.

Results

After applying the re-censoring procedure to the patients in the control arm, the number of events in the control arm is reduced from [redacted] to [redacted] in KEYNOTE-042, and the number of events is reduced from [redacted] to [redacted] in the control arm from KEYNOTE-407.

Table 1 shows the log-logistic model parameters by treatment arm regarding OS adjusted for treatment switching using 2-Stage model with re-censoring for KEYNOTE-042 and KEYNOTE-407. Table 2 presents the estimated overall survival and the corresponding hazard ratios at timepoints 1, 3, 6, 9, 12, 15, 18, 21 and 24 months. The HR (95% CI) for the comparison of pembrolizumab monotherapy vs. pembrolizumab + chemotherapy decreases over time, i.e., from [redacted] ([redacted]) at month 1 to [redacted] ([redacted]) at month 24.

Table 1. Model Parameters of the Log-logistic distribution Analysis of Overall Survival for Treatment Switch Using Two-stage Model With Re-censoring (Intention-to-Treat Population, TPS ≥ 50%)

		Parameters of the model (Log-Logistic)[a]		
		alpha (variance) (95% CI)	**lambda (variance) (95% CI)**	**corr(alpha,lambda) (covariance)**
Study 042[c]	Pembrolizumab Monotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b,e]	[redacted]	[redacted]	[redacted]
Study 407[d]	Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b,e]	[redacted]	[redacted]	[redacted]

a: Based on the hazard function following log-logistic distribution
b: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin
c: Database Cutoff Date: 04SEP2018
d: Database Cutoff Date: 09MAY2019
e: Two-stage model is used to adjust for the effect of treatment switch from chemotherapy to Pembrolizumab 200 mg Q3W or other anti-PD1/PD-L1 therapies. Re-censoring was performed.
corr: correlation

Table 2. Analysis of Overall Survival using model based on the Log-Logistic distribution Adjusting for Treatment Switch in Control Arm Using 2-Stage Model With Re-censoring (Intention-to-Treat Population, TPS ≥ 50%)

	Study 042[a]			Study 407[b]			ITC
	Pembrolizumab Monotherapy	Chemotherapy[c,f]		Pembrolizumab + Chemotherapy	Chemotherapy[c,f]		
Time point (months)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	HR[e] (95% CI)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	HR[e] (95% CI)	HR[d] (95% CI)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: 04SEP2018

b: Database Cutoff Date: 09MAY2019

c: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin

d: Bucher methodology using separate study results (estimate and its standard error) with a common control arm to perform indirect comparison of effect of monotherapy (P042) vs pembrolizumab combination (P407)

e: Based on the estimates obtained from the hazard function at treatment arm with the hazard function following a log-logistic distribution

f: Two-stage model is used to adjust for the effect of treatment switch from chemotherapy to Pembrolizumab 200 mg Q3W or other anti-PD1/PD-L1 therapies. Re-censoring was performed.

Figure 1 and

Figure 2 display the corresponding fitted curves alongside the Kaplan-Meier curves for KEYNOTE-042 and KEYNOTE-407.

Figure 1. Overall Survival Adjusted for Treatment Switch in Control Arm Using 2-Stage Model with Recensoring (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 042)

Figure 2. Overall Survival Adjusted for Treatment Switch in Control Arm Using 2-Stage Model with Recensoring (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 407)

It is evident that re-censoring resulted in an important loss of information, both in terms of follow-time as well as the number of events. For both studies, there was a high number of re-censored events. Due to the substantial impact of re-censoring, the results from 2-stage analyses with re-censoring are to be considered with great caution.

B5. Please provide more information about the switching analyses which have been undertaken:

a) Which accelerated failure time (AFT) model was used to estimate the time ratio/acceleration factor associated with switching? Were the results sensitive to the AFT model used?

b) Which covariates were included in the AFT model?

c) What was the model output? Please report coefficients for all the covariates in the model

d) Were data on any important variables missing?

e) What was the time ratio/AF estimated?

f) How has uncertainty associated with the adjustment been incorporated into the subsequent survival modelling and indirect comparison?

The answer to this question was submitted in response to the clarification questions on 19th March 2020.

Indirect comparison of KEYNOTE-407 and KEYNOTE-042 (Section A.7.1, pages 47 to 65)

B6. Priority question. Given that the baseline model for the indirect comparison is assumed to follow a log logistic distribution (an AFT model), the use of hazard ratios is not appropriate. Please repeat the indirect comparison of the KEYNOTE-407 and KEYNOTE-042 data using the failure odds transformation of the survival functions (see equation below), with treatment effects estimated for "ln" (l)+β

$$\ln\big(O(t)\big) = \ln(l) + \beta \times \ln(t)$$

While it is correct that the log-logistic distribution was selected, it was not used in the context of the AFT (Accelerated Failure Time) model. A saturated model was used (2 parameters per treatment arm). In each trial, the AFT model would provide 3 parameters while the saturated model would have 4 parameters. Therefore, the odds ratio per trial will vary with time in the saturated model while it would not in the

AFT model (this AFT model would be a proportional odds model per construction, and the treatment effect would be a single odds ratio independent of time).

Considering the survival time follows a log-logistic distribution described as

$$S(x) = \frac{1}{1 + \lambda x^{\alpha}}$$

then log odds of failure could be obtained as below.

$$Log\left(\frac{1-S}{S}\right) = Log(\lambda) + \alpha Log(x)$$

Results

Table 3 shows the log-logistic model parameters by treatment arm regarding overall survival in KEYNOTE-042 and KEYNOTE407. Table 4 presents the estimated overall survival and the corresponding odds ratios of failure at timepoints 1, 3, 6, 9, 12, 15, 18, 21 and 24 months. The odds ratios of failure (95% CI) for the comparison of pembrolizumab monotherapy vs. pembrolizumab + chemotherapy decreases over time, i.e., from [redacted] ([redacted]) at month 1 to [redacted] ([redacted]) at month 24.

Table 3. Model Parameters of Overall Survival using the Log-Logistic distribution (Intention-to-Treat Population, TPS ≥ 50%)

		Parameters of the model (Log-Logistic)[a]		
		alpha (variance) (95% CI)	**lambda (variance) (95% CI)**	**corr(alpha,lambda) (covariance)**
Study 042[c]	Pembrolizumab Monotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b]	[redacted]	[redacted]	[redacted]
Study 407[d]	Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b]	[redacted]	[redacted]	[redacted]

a: Based on the hazard function following log-logistic distribution
b: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin
c: Database Cutoff Date: 04SEP2018
d: Database Cutoff Date: 09MAY2019
corr: correlation

Table 4. Analysis of Overall Survival using model based on the Log-Logistic distribution (Intention-to-Treat Population, TPS ≥ 50%)

	Study 042[a]			Study 407[b]			ITC
	Pembrolizumab Monotherapy	Chemotherapy[c]		Pembrolizumab + Chemotherapy	Chemotherapy[c]		
Time point (months)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	Failure Odds Ratio[e] (95% CI)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	Failure Odds Ratio[e] (95% CI)	Failure Odds Ratio[d] (95% CI)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B7. Please clarify the relevance of the number of patients after 24 months (which have been currently excluded from the indirect comparison). Please explain why treatment effects have not been estimated from the fitted parametric (log-logistic) models.

The answer to this question was submitted in response to the clarification questions on 19th March 2020.

B8. Priority question. In the description of the indirect comparison, please include the following:

a) Please include a discussion around potential treatment effect modifiers and assess whether these are different between the two studies.

For the ITC analyses presented in the submission using the log-logistic distribution, it was implicitly assumed that there were no important differences between trials impacting study outcome. Additional sensitivity analyses have been performed in which the populations of both trials and four treatment arms were adjusted by balancing out the covariates expected to influence the outcome.

A set of covariates was identified as potential effect modifiers, primarily based on clinical input. More specifically, ECOG PS (0 vs. 1 or 2), smoking status, age, gender and tumour size were considered as potential effect modifiers.

The Inverse Probability of Treatment Weighting (IPTW) methodology was applied to balance out the 4 treatment arms. The predicted probability of receiving a specific treatment for each subject, referred as propensity score, was calculated using a multinomial logistic regression with these effect modifiers as covariates. The inverse of the propensity score calculated for each subject represented the weight for that subject. The resulting weights were also stabilized as follows: the weight for each subject was multiplied by the marginal probability of the treatment that this subject received. The marginal probability of each treatment was estimated by the proportion of subjects in this treatment arm among the overall population.

This technique does not only reduce the imbalance of populations between trials, but also between the arms within each trial.

The quality of the balancing was checked:

- By summarizing the covariates considered per trial and per treatment arm (N and percentages or mean) before and after weighting.

- By reporting the standardized absolute difference in mean for continuous covariate and in proportion for different categories of the baseline factors. The

maximum standardized absolute difference among the pairwise comparisons was reported as there are 4 treatment arms. This statistic was provided for each category of each of the different baseline factors. The standardized absolute differences are equal for the 2 categories of a binary baseline variable; therefore, the results are displayed only for one category. Standardized absolute differences before and after weighting are provided.

Afterwards the indirect treatment comparison of pembrolizumab monotherapy (KEYNOTE-042) versus pembrolizumab + chemotherapy (KEYNOTE-407) in overall survival is performed similarly as previously described with the exception that the weighted maximum likelihood and the robust sandwich estimate of the covariance matrix is used to estimate survival time following log-logistic distribution.

Results

Subjects Baseline Characteristics and Weights Summary

Table 5 summarizes the weight calculated for each subject and used to balance out the subject characteristics across the 4 treatment arms. The weights were generally stable and ranged from [redacted] to [redacted] with a median of [redacted]. Overall, the range of weights was highest for subjects in the pembrolizumab + chemotherapy arm of KEYNOTE-407 (i.e., [redacted] to [redacted]); the medians of weights were generally similar in all 4 treatment arms.

Table 5. Subject Characteristics Inverse Probability of Treatment Weight (Intention-to-Treat Population, TPS ≥ 50%)

	Study 407[a]		Study 042[b]		
	Pembrolizumab + Chemotherapy	Chemotherapy	Pembrolizumab Monotherapy	Chemotherapy	Total
Subjects in population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inverse Probability of Treatment Weight					
Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: 09MAY2019
b: Database Cutoff Date: 04SEP2018
TPS: Tumor Proportion Score.

Table 6 shows the baseline characteristics before weighting. Imbalances in distribution were observed for all the selected effect modifiers: ECOG PS (0 vs. 1 or 2), smoking status (never vs. former/current), gender (female vs. male), baseline tumour size and age.

Baseline characteristics after weighting were very well balanced across the 4 arms as shown in Table 7. The maximum of standardized absolute differences among all pairwise imbalance assessments between the 4 treatment arms is reported in

Table **8**. Prior to weighting, the highest maximum of standardized absolute differences were observed for baseline tumour size, reaching a value of [redacted]. The standardized absolute differences confirmed that the initial imbalances for some of the factors were reduced after weighting.

Table 6. Subject Characteristics Before Weighting (Intention-to-Treat Population, TPS ≥ 50%)

	Before Weighting			
	Study 407[a]		Study 042[b]	
	Pembrolizumab + Chemotherapy (N=69)	Chemotherapy (N=69)	Pembrolizumab Monotherapy (N=89)	Chemotherapy (N=93)
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Tumor Size	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]	[redacted]
F	[redacted]	[redacted]	[redacted]	[redacted]
M	[redacted]	[redacted]	[redacted]	[redacted]
ECOG (%)	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]
1 or 2	[redacted]	[redacted]	[redacted]	[redacted]
Smoker status	[redacted]	[redacted]	[redacted]	[redacted]
Former/Current Smoker	[redacted]	[redacted]	[redacted]	[redacted]
Never Smoked	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: 09MAY2019
b: Database Cutoff Date: 04SEP2018
ECOG: European Cooperative Oncology Group; TPS: Tumor Proportion Score.

Table 7. Subject Characteristics After Weighting (Intention-to-Treat Population, TPS ≥ 50%)

	After Weighting			
	Study 407[a]		Study 042[b]	
	Pembrolizumab + Chemotherapy (N=69)	Chemotherapy (N=69)	Pembrolizumab Monotherapy (N=89)	Chemotherapy (N=93)
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Tumor Size	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]	[redacted]
F	[redacted]	[redacted]	[redacted]	[redacted]
M	[redacted]	[redacted]	[redacted]	[redacted]
ECOG (%)	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]
1 or 2	[redacted]	[redacted]	[redacted]	[redacted]
Smoker status	[redacted]	[redacted]	[redacted]	[redacted]
Former/Current Smoker	[redacted]	[redacted]	[redacted]	[redacted]
Never Smoked	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: 09MAY2019
b: Database Cutoff Date: 04SEP2018
ECOG: European Cooperative Oncology Group; TPS: Tumor Proportion Score.

Table 8. The maximum standardized difference among all the pairwise treatment arms ITT Population TPS≥50%

	Maximum standardized difference across all treatment arms	
	Before Weighting	After Weighting
Age	[redacted]	[redacted]
ECOG	[redacted]	[redacted]
0 (0 vs 1 or 2)	[redacted]	[redacted]
Smoker status	[redacted]	[redacted]
Former/Current Smoker (Former/Current Smoker vs Never Smoked)	[redacted]	[redacted]
Sex	[redacted]	[redacted]
F (F vs M)	[redacted]	[redacted]
Baseline Tumor Size	[redacted]	[redacted]

ECOG: European Cooperative Oncology Group; TPS: Tumor Proportion Score.

Overall Survival ITT – Population Adjusted

Table 9 shows the log-logistic model parameters by treatment arm regarding overall survival after balancing the populations from KEYNOTE-042 and KEYNOTE407 through IPTW. Table 10 presents the estimated overall survival and the corresponding hazard ratios at timepoints 1, 3, 6, 9, 12, 15, 18, 21 and 24 months. The HR (95% CI) for the comparison of pembrolizumab monotherapy vs. pembrolizumab + chemotherapy decreases over time, i.e., from [redacted] ([redacted]) at month 1 to [redacted] ([redacted]) at month 24.

Table 9. Model Parameters of the model based on the Log-logistic distribution Population-Adjusted Analysis of Overall Survival (Intention-to-Treat Population, TPS ≥ 50%)

		Parameters of the model (Log-Logistic)[a]		
		alpha (variance) (95% CI)	**lambda (variance) (95% CI)**	**corr(alpha,lambda) (covariance)**
Study 042[c]	Pembrolizumab Monotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b]	[redacted]	[redacted]	[redacted]
Study 407[d]	Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b]	[redacted]	[redacted]	[redacted]

a: Based on the hazard function following log-logistic distribution
b: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin
c: Database Cutoff Date: 04SEP2018
d: Database Cutoff Date: 09MAY2019
corr: correlation

Table 10. Analysis of Overall Survival using model based on the Log-Logistic distribution Population-Adjusted Analysis (Intention-to-Treat Population, TPS ≥ 50%)

	Study 042[a]			Study 407[b]			ITC
	Pembrolizumab Monotherapy	Chemotherapy[c]		Pembrolizumab + Chemotherapy	Chemotherapy[c]		
Time point (months)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	HR[e] (95% CI)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	HR[e] (95% CI)	HR[d] (95% CI)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: 04SEP2018

b: Database Cutoff Date: 09MAY2019

c: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin

d: Bucher methodology using separate study results (estimate and its standard error) with a common control arm to perform indirect comparison of effect of monotherapy (P042) vs pembrolizumab combination (P407)

e: Based on the estimates obtained from the hazard function at treatment arm with the hazard function following a log-logistic distribution

Figure 3 and Figure 4 display the corresponding fitted curves alongside the Kaplan-Meier curves for KEYNOTE-042 and KEYNOTE-407 after balancing the populations through IPTW.

Figure 3. Overall Survival Kaplan-Meier curves and Fit of the Log-logistic Distribution Population-Adjusted Analysis Based on Study 042 (ITT Population, TPS ≥ 50%)

Figure 4. Overall Survival Kaplan-Meier curves and Fit of the Log-logistic Distribution Population-Adjusted Analysis Based on Study 407 (ITT Population, TPS ≥ 50%)

Overall Survival Adjusted for Switchover using 2-Stage model without re-censoring – Population Adjusted

Table 11 shows the log-logistic model parameters by treatment arm regarding overall survival adjusted treatment switching using 2-Stage model after balancing the populations from KEYNOTE-042 and KEYNOTE407 through IPTW. Table 12 presents the estimated overall survival and the corresponding hazard ratios at timepoints 1, 3, 6, 9, 12, 15, 18, 21 and 24 months. The HR (95% CI) for the comparison of pembrolizumab monotherapy vs. pembrolizumab + chemotherapy decreases over time, i.e., from [redacted] at month 1 to [redacted] at month 24.

Table 11. Model Parameters of the Log-logistic distribution Population-Adjusted Analysis of Overall Survival for Treatment Switch Using Two-stage Model Without Re-censoring (Intention-to-Treat Population, TPS ≥ 50%)

		Parameters of the model (Log-Logistic)[a]		
		alpha (variance) (95% CI)	**lambda (variance) (95% CI)**	**corr(alpha,lambda) (covariance)**
Study 042[c]	Pembrolizumab Monotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b,e]	[redacted]	[redacted]	[redacted]
Study 407[d]	Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy[b,e]	[redacted]	[redacted]	[redacted]

a: Based on the hazard function following log-logistic distribution
b: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin
c: Database Cutoff Date: 04SEP2018
d: Database Cutoff Date: 09MAY2019
e: Two-stage model is used to adjust for the effect of treatment switch from chemotherapy to Pembrolizumab 200 mg Q3W or other anti-PD1/PD-L1 therapies. No re-censoring was performed.
corr: correlation

Table 12. Analysis of Overall Survival using model based on the Log-Logistic distribution Population-Adjusted Analysis for Treatment Switch Using Two-stage Model Without Re-censoring (Intention-to-Treat Population, TPS ≥ 50%)

	Study 042[a]			Study 407[b]			ITC
	Pembrolizumab Monotherapy	Chemotherapy[c,f]		Pembrolizumab + Chemotherapy	Chemotherapy[c,f]		
Time point (months)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	HR[e] (95% CI)	Overall Survival[e] in % (95% CI)	Overall Survival[e] in % (95% CI)	HR[e] (95% CI)	HR[d] (95% CI)
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a: Database Cutoff Date: 04SEP2018

b: Database Cutoff Date: 09MAY2019

c: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin

d: Bucher methodology using separate study results (estimate and its standard error) with a common control arm to perform indirect comparison of effect of monotherapy (P042) vs pembrolizumab combination (P407)

e: Based on the estimates obtained from the hazard function at treatment arm with the hazard function following a log-logistic distribution

f: Two-stage model is used to adjust for the effect of treatment switch from chemotherapy to Pembrolizumab 200 mg Q3W or other anti-PD1/PD-L1 therapies. No re-censoring was performed.

Figure 5 and Figure 6 display the corresponding fitted curves alongside the Kaplan-Meier curves for KEYNOTE-042 and KEYNOTE-407 after balancing the populations through IPTW.

Figure 5. Population-Adjusted Analysis of Overall Survival for Treatment Switch Using Two-stage Model Without Re-censoring Kaplan-Meier curves and Fit of the Log-Logistic Distribution Based on Study 042 (Intention-to-Treat Population, TPS ≥ 50%)

Figure 6. Population-Adjusted Analysis of Overall Survival for Treatment Switch Using Two-stage Model Without Re-censoring Kaplan-Meier curves and Fit of the Log-logistic Distribution Based on Study 407(Intention-to-Treat Population, TPS ≥ 50%)

b) Please ensure that the derivation of the standard errors of the log odds are appropriately explained.

The Delta method is used for approximating the standard errors of parameters (scale, shape) of log-logistic distribution. This is applied to estimate the log odds presented in response to questions B.6, as well as survival time following the log-logistic distribution reported in ITC report referenced within the submission.

c) When presenting the unadjusted and adjusted OS and PFS from the indirect comparison (Figures 11-16), please ensure that the model-based cumulative survival probabilities are shown over a longer time horizon.

With the model parameters provided in the submission dossier, page 53 for unadjusted overall survival, page 58 for adjusted overall survival using 2-stage, and page 62 for progression-free survival, the fitted survival curve following log-logistic distribution can be plotted until any timepoint.

Figure 7 and Figure 8 display the Kaplan-Meier curves and the log-logistic fits up to month 42 for overall survival in KEYNOTE-042 and KEYNOTE-407 respectively.

Figure 7. Overall Survival (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 042)

Figure 8. Overall Survival (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 407)

Figure 9 and Figure 10 display the Kaplan-Meier curves and the log-logistic fits up to month 42 for overall survival adjusted treatment switching using 2-Stage model in KEYNOTE-042 and KEYNOTE-407 respectively.

Figure 9. Overall Survival Adjusted for Treatment Switch to Pembrolizumab 200 mg Q3W or Other Anti-PD1/PD-L1 Therapies in Control Arm Using 2-Stage Analysis Without Recensoring (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 042)

Figure 10. Overall Survival Adjusted for Treatment Switch to Pembrolizumab 200 mg Q3W or Other Anti-PD1/PD-L1 Therapies in Control Arm Using 2-Stage Analysis Without Recensoring (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 407)

Figure 11 and Figure 12 display the Kaplan-Meier curves and the log-logistic fits up to month 42 for progression-free survival adjusted in KEYNOTE-042 and KEYNOTE-407 respectively.

Figure 11. Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 042)

Figure 12. Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 (Kaplan-Meier + Fit of the Log-logistic Distribution) ITT Population, TPS ≥ 50% (Study 407)

Survival analysis (Appendices)

B9. Priority question. Please explain how plausibility was taken into account when selecting preferred survival models for the subgroup analyses.

The answer to this question was submitted in response to the clarification questions on 19th March 2020.

B10. Priority question. Given that KEYNOTE-407 allows for a maximum of 35 cycles of pembrolizumab (~2 years), please clarify why a parametric model has been fitted to extrapolate time to treatment discontinuation for the intervention group of the model

The answer to this question was submitted in response to the clarification questions on 19th March 2020.

PD-L1 subgroup results (executable model)

B11. Priority question. Please clarify which model user settings need to be applied to generate the incremental cost-effectiveness ratios (ICERs) for the PD-L1 subgroups using the updated model.

The answer to this question was submitted in response to the clarification questions on 19th March 2020.

Section C: Textual clarification and additional points

None.

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]

Evidence Review Group Report

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Date completed	Original report completed 30th March 2020. Factual accuracy check amendments included December 2020. Updated executive summary added April 2021.

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number NIHR130472.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Matt Stevenson, ScHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting 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:

Tappenden P, Navega Biz A, Uttley L, Stevens JW. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review: Evidence Review Group Report. School of Health and Related Research (ScHARR), University of Sheffield; 2020.

Contributions of authors

Lesley Uttley summarised and critiqued the clinical effectiveness evidence reported within the company's submission. Paul Tappenden and Aline Navega Biz critiqued the health economic analysis submitted by the company and undertook additional exploratory analyses. John Stevens critiqued the statistical aspects of the submission. All authors were involved in drafting and commenting on the final report.

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Abbreviations

2L	Second-line
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CDF	Cancer Drugs Fund
CDF-CS	Company's submission for CDF review
CI	Confidence interval
cPAS	Comparator Patient Access Scheme
CS	Company's submission
ECOG	European Cooperative Oncology Group
EoL	End-of-Life
ERG	Evidence Review Group
HR	Hazard ratio
IA2	Interim Analysis 2
ICER	Incremental cost-effectiveness ratio
irAE	Immune-related adverse event
ITT	Intention-to-treat
KM	Kaplan-Meier
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSCLC	Non-small-cell lung cancer
OS	Overall survival
PAS	Patient Access Scheme
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
QALY	Quality-adjusted life year
RR	Relative risk
SAE	Serious adverse event
SEER	Surveillance, Epidemiology and End Results
SmPC	Summary of Product Characteristics
SWQ	South-West quadrant
TA	Technology Appraisal
TPS	Tumour proportion score
TTD	Time to treatment discontinuation
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

1.1 Overview of the ERG's key issues

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision-making. 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 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. The results of the ERG's exploratory analyses are presented in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report. All issues identified represent the ERG's view, not the opinion of NICE.

The key issues identified by the ERG are summarised in Table 1.

Table 1: Overview of the ERG's key issues

ID3835	Summary of issue	Report sections
Issue 1	Uncertainty surrounding the long-term treatment effect of pembrolizumab combination therapy on PFS and OS	3.2, 4.4.2, 4.4.3
Issue 2	No additional safety data are presented in the CDF-CS	3.2.3
Issue 3	Committee's preferred assumptions regarding subsequent immunotherapy use do not reflect experience of KEYNOTE-407	4.4.6
Issue 4	The indirect comparison for the PD-L1 TPS≥50% subgroup presented in the CDF-CS is not robust	4.4.7
Issue 5	Uncertainty concerning whether pembrolizumab combination therapy meets NICE's End-of-Life criteria	5

PFS - progression-free survival; OS - overall survival; PD-L1 - programmed death ligand 1; TPS - tumour proportion score; NICE - National Institute for Health and Care Excellence; CDF-CS - company's submission for CDF review

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the additional cost for every QALY gained.

Overall, the company's model suggests that pembrolizumab combination therapy affects QALYs by:

- Increasing overall survival (OS) compared with standard chemotherapy
- Increasing time spent alive and progression-free compared with standard chemotherapy.

Overall, the company's model suggests that pembrolizumab combination therapy affects costs by:

- Increasing first-line drug treatment costs, specifically due to the higher acquisition costs of pembrolizumab combination therapy compared with standard chemotherapy

- Reducing the costs associated with subsequent-line therapies, in particular, those associated with second-line immunotherapies.

The modelling assumptions that have the greatest effect on the ICER are:

- The parametric survival models applied to progression-free survival (PFS) and OS
- Assumptions regarding the use of treatments given following disease progression
- The population in whom treatment with pembrolizumab combination therapy is considered – the ICERs vary considerably between the subgroups of patients with programmed death ligand 1 (PD-L1) tumour proportion scores (TPS) of <1%, 1-49% and ≥50%.

1.3 Background and decision problem

This ERG report presents a summary and critique of additional evidence submitted by the company to inform a Cancer Drugs Fund (CDF) guidance review of pembrolizumab in combination with carboplatin and paclitaxel for the treatment of untreated metastatic squamous non-small-cell lung cancer (NSCLC).

In September 2019, the National Institute for Health and Care Excellence (NICE) published the following guidance recommendation: *"Pembrolizumab, with carboplatin and paclitaxel, is recommended for use within the Cancer Drugs Fund as an option for untreated metastatic squamous non-small-cell lung cancer (NSCLC) in adults only if: pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier if disease progresses, and the company provides pembrolizumab according to the managed access agreement."* During the original NICE appraisal (Technology Appraisal Guidance Number 600 [TA600]), the key clinical evidence for pembrolizumab combination therapy was based on Interim Analysis 2 (IA2) of KEYNOTE-407 – a Phase III multi-centre, triple-blind, randomised controlled trial (RCT) comparing pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel (pembrolizumab combination therapy) versus placebo plus carboplatin and paclitaxel/nab-paclitaxel (control). The data from IA2 were immature (data cut-off April 2018), which resulted in considerable uncertainty surrounding the magnitude and duration of the clinical benefit of pembrolizumab combination therapy relative to standard treatments. In February 2020, the company submitted additional evidence from the final analysis of KEYNOTE-407 (data cut-off May 2019) to inform this CDF review; the final data-cut provides an additional [redacted] months of follow-up compared with IA2. The company's additional evidence includes a written submission (hereafter referred to as the "CDF-CS") and an updated health economic model which includes data from the final analysis of KEYNOTE-407. Overall, the ERG considers the CDF-CS and the accompanying model to be in line the terms of engagement for this CDF guidance review.

1.4 Summary of clinical effectiveness evidence submitted by the company

Within the intention-to-treat (ITT) population of KEYNOTE-407, median overall survival (OS) was 5.5 months longer in the pembrolizumab combination group compared with the control group (17.1 months versus 11.6 months). The hazard ratio (HR) for OS was 0.71 (95% confidence interval (CI): 0.58, 0.88; p=[redacted]) in favour of pembrolizumab combination therapy. A statistically significant improvement in OS for pembrolizumab combination therapy was reported for the subgroup of patients with PD-L1 TPS 1-49% (p=[redacted]), but not within the TPS <1% or TPS ≥50% groups (p>[redacted]).

Within the ITT population, median PFS was 2.9 months longer in the pembrolizumab combination group compared with the control group (8.0 months versus 5.1 months). The HR for PFS was 0.57 (95% CI: 0.47, 0.69; p<[redacted]) in favour of pembrolizumab combination therapy. Statistically significant improvements in PFS were reported for pembrolizumab combination therapy for all PD-L1 TPS subgroups (p<[redacted]).

The CDF-CS does not provide any additional evidence relating to adverse events (AEs) from the final data-cut of KEYNOTE-407.

The key issues relating to the clinical evidence for pembrolizumab combination therapy also impact on the company's updated cost-effectiveness analysis; hence, all key issues are presented together in Section 1.5.

1.5 Summary of cost-effectiveness evidence submitted by the company

As part of the CDF review, the company updated their economic model and fitted parametric survival models to the final data-cut of KEYNOTE-407. In line with the terms of engagement, the starting point for the company's updated economic model is "ERG pessimistic analysis 6b" within TA600. Results are presented for the overall ITT population and for each of the three PD-L1 TPS subgroups. The company's updated health economic model includes the following features:

- OS – log-logistic models were fitted to the final data-cut of KEYNOTE-407 (no cut-point, models fitted independently to data for each treatment group).
- PFS – based on a hybrid approach using Kaplan-Meier estimates followed by log-normal models fitted to the final data-cut of KEYNOTE-407 (26-week cut-point, models fitted independently to data for each treatment group).
- Time to treatment discontinuation (TTD) – a generalised gamma model was fitted to data from the final data-cut of KEYNOTE-407 for pembrolizumab (truncated after a maximum treatment duration of 35 cycles); observed Kaplan-Meier estimates were updated for the standard care group.

- Subsequent treatments – probabilities of receiving second-line treatments were updated using the final data-cut of KEYNOTE-407; the durations of second-line atezolizumab and pembrolizumab in the standard care group were based on the OAK trial and the KEYNOTE-010 trial, respectively (previously based on KEYNOTE-407).
- Health-related quality of life – health utilities were defined according to the model health states. The utility value for the progression-free state was based on KEYNOTE-407; the utility value for the post-progression state was based on the TOPICAL trial (Khan *et al*) with adjustment for the proportion of patients receiving second-line immunotherapy, based on the same assumptions as ERG pessimistic analysis 6b.
- Indirect comparison in the PD-L1 TPS ≥50% subgroup – time-varying HRs were derived from KEYNOTE-407 and KEYNOTE-042, with statistical adjustment for imbalances in second-line immunotherapy use in the chemotherapy arms of each trial.

Based on the deterministic version of the company's model for the ITT population, pembrolizumab combination therapy is estimated to generate an additional [redacted] QALYs at an additional cost of [redacted] compared with standard care; the corresponding ICER is estimated to be £38,090 per QALY gained. The probabilistic version of the company's model produced a similar ICER of £38,834 per QALY gained. The ICERs for pembrolizumab combination therapy versus standard care within the PD-L1 TPS <1% and 1-49% subgroups are estimated to be £48,742 and £28,190 per QALY gained, respectively. Within the PD-L1 TPS ≥50% subgroup, pembrolizumab combination therapy is estimated to generate less health and lower costs relative to pembrolizumab monotherapy: the ICER for pembrolizumab combination therapy versus pembrolizumab monotherapy is estimated to be £18,398 saved per QALY lost.

Issue 1: Uncertainty surrounding the long-term treatment effect of pembrolizumab combination therapy on PFS and OS

Report section	3.2, 4.4.2, 4.4.3
Description of issue and why the ERG has identified it as important	The final data-cut of KEYNOTE-407 is considerably more mature than IA2, including an additional [redacted] deaths and an additional [redacted] PFS events. There remains uncertainty regarding the long-term treatment effect of pembrolizumab combination therapy on PFS and OS, as few patients remain at risk beyond the maximum treatment duration of 35 cycles (approximately 2 years). The ERG considers that the company's decision to apply the log-logistic model for OS in both groups is reasonable. The long-term modelled OS estimates for the pembrolizumab combination therapy group are broadly consistent with the pessimistic estimates obtained from the ERG's clinical advisor 3 during TA600. The long-term modelled OS estimates for the standard care group are similar to or within the ranges provided by all clinical advisors to NICE and the ERG during TA600. The ERG notes however that all of these estimates are subject to uncertainty and the use of most of the alternative parametric survival models increases the ICER for pembrolizumab combination therapy.

What alternative approach has the ERG suggested?	The ERG has undertaken additional sensitivity analyses using alternative parametric survival models for OS and PFS.
What is the expected effect on the cost-effectiveness estimates?	Within the ITT population, the ERG's preferred analysis suggests that the ICER for pembrolizumab combination therapy versus standard care is £47,911 per QALY gained. This analysis applies the log-logistic model for OS and a hybrid Kaplan-Meier and log-normal model for PFS. The ERG's additional sensitivity analyses using alternative parametric survival models for OS lead to ICERs ranging from £47,586 per QALY gained (log-normal) to £99,539 per QALY gained (Gompertz). The ERG's additional sensitivity analyses suggest that the model results are comparatively less sensitive to the choice of PFS model, with ICERs ranging from £47,911 per QALY gained (log-normal) to £60,229 per QALY gained (exponential).
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up of KEYNOTE-407 would reduce uncertainty surrounding OS and PFS.

Issue 2: No additional safety data are presented in the CDF-CS

Report section	3.2.3
Description of issue and why the ERG has identified it as important	No additional information on AEs has been provided from the final data-cut of KEYNOTE-407. Whilst this is in line with the terms of engagement for this CDF guidance review, the long-term toxicity profile of pembrolizumab combination therapy remains uncertain.
What alternative approach has the ERG suggested?	The ERG would have preferred additional safety data from the final data-cut of KEYNOTE-407 to be included in the company's updated analysis for this CDF review.
What is the expected effect on the cost-effectiveness estimates?	The impact of including longer-term safety data from KEYNOTE-407 on the ICER for pembrolizumab combination therapy is unknown.
What additional evidence or analyses might help to resolve this key issue?	The inclusion of updated safety data in the company's model is required to understand its impact on the ICER for pembrolizumab combination therapy. However, this was not a requirement of the terms of engagement for this CDF review.

Issue 3: Committee's preferred assumptions regarding subsequent immunotherapy use do not reflect experience of KEYNOTE-407

Report section	4.4.6
Description of issue and why the ERG has identified it as important	The committee's preferred assumptions regarding subsequent-line immunotherapy use in the standard chemotherapy group, which were introduced into the model following the technical engagement process for TA600, are inconsistent with the experience of the KEYNOTE-407 trial, as they apply the costs of immunotherapy to all standard care patients who receive subsequent-line treatment, yet around [redacted] of these patients received chemotherapy alone. Applying updated estimates of subsequent-line treatments which better reflect

	the final data-cut of KEYNOTE-407 increases the ICER for pembrolizumab combination therapy.
What alternative approach has the ERG suggested?	The ERG has amended the company's model to include the distribution of all subsequent-line therapies received in KEYNOTE-407 together with an assumption that of those patients in the standard care group who received a subsequent-line immunotherapy, 75% receive atezolizumab and the remaining 25% receive pembrolizumab.
What is the expected effect on the cost-effectiveness estimates?	Within the ITT population, the re-estimation of the distribution of subsequent-line therapies increases the company's base case ICER from £38,090 to £45,240 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	No additional analyses are required beyond those presented within this report.

Issue 4: The indirect comparison for the PD-L1 TPS≥50% subgroup presented in the CDF-CS is not robust

Report section	4.4.7
Description of issue and why the ERG has identified it as important	The CDF-CS presents an indirect comparison of pembrolizumab combination therapy versus pembrolizumab monotherapy in the PD-L1 TPS ≥50% subgroup based on an analysis of data from KEYNOTE-407 and KEYNOTE-042. This is subject to several problems, including: • The company's adjustment for treatment switching does not include re-censoring and as such may be prone to informative censoring. • The CDF-CS mentions an imbalance in the use of immunotherapies between KEYNOTE-042 and KEYNOTE-047, but does not discuss potential treatment effect modifiers and their potential impact on the results of the indirect comparison. • The company's preferred survival model is a log-logistic model and the company summarised the results of the indirect comparison using time-varying HRs. A log-logistic model is an acceleration failure time (AFT) model and HRs are not a natural scale on which to describe relative treatment effects.
What alternative approach has the ERG suggested?	During the clarification process, the ERG requested that the company undertake a new indirect comparison using the failure odds transformation of the survival functions, together with some discussion of potential treatment effect modifiers. The ERG also requested additional treatment switching analyses which include re-censoring.
What is the expected effect on the cost-effectiveness estimates?	The company was unable to provide the ERG's requested analyses within the timescales available for this ERG report. The impact on the ICER for pembrolizumab combination therapy in the PD-L1 TPS ≥50% subgroup is unknown. It is expected that the analyses will be provided by the company at a later timepoint in the appraisal process.
What additional evidence or analyses might help to resolve this key issue?	

Issue 5: Uncertainty concerning whether pembrolizumab combination therapy meets NICE's End-of-Life criteria

Report section	5
Description of issue and why the ERG has identified it as important	Median survival in the control arm of KEYNOTE-407 was 11.6 months. The company's base case model suggests that mean survival in the standard care group is 2.26 years. The survival distribution for the standard care group suggests OS probabilities at 1- and 2-years of 0.51 and 0.28, respectively, with a small proportion of long-term survivors remaining alive at 10-years (probability=0.04). Overall, the ERG is uncertain whether NICE's End-of-Life criteria are met.
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up of KEYNOTE-407 would reduce uncertainty surrounding long-term projections of OS within the ITT population and the PD-L1 TPS subgroups.

1.6 Summary of ERG's preferred assumptions and resulting ICER

The results of the ERG's exploratory analyses for the overall population are summarised in Table 2; these results are presented as individual changes relative to the company's base case analysis. The results for the ERG's preferred analyses for the three PD-L1 TPS subgroups are summarised in Table 3. Within the ITT population, the deterministic version of the ERG's preferred model suggests that the ICER for pembrolizumab combination therapy versus standard care is £47,911 per QALY gained. The probabilistic version of the model suggests a lower ICER of £46,997 per QALY gained. The deterministic ICERs for pembrolizumab combination therapy versus standard care were estimated to be £62,619 and £37,669 per QALY gained for the PD-L1 TPS <1% and TPS 1-49% subgroups, respectively. Within the TPS ≥50% subgroup, the ICER for pembrolizumab combination therapy versus pembrolizumab monotherapy was estimated to be £16,097 saved per QALY lost.

Table 2: Summary of ERG preferred assumptions and ICERs, ITT population

Scenario	Incremental QALYs	Incremental cost	ICER (change from company's updated base case)
Company's base case model	[redacted]	[redacted]	**£38,090**
ERG exploratory analysis 1 – Kaplan-Meier estimates for TTD	[redacted]	[redacted]	**£39,847** (+£1,757)
ERG exploratory analysis 2 – Updated distribution of subsequent-line therapies	[redacted]	[redacted]	**£45,240** (+£7,150)
ERG exploratory analysis 3 – Inclusion of treatment effect waning for PFS	[redacted]	[redacted]	**£38,872** (+£782)
ERG exploratory analysis 4 – ERG preferred analysis (ERG analysis 1 to 3 combined)	[redacted]	[redacted]	**£47,911** (+£9,821)

ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year; ITT - intention-to-treat; TTD - time to treatment discontinuation; PFS - progression-free survival; ERG - Evidence Review Group

Table 3: Summary of ERG preferred ICERs, PD-L1 TPS subgroups

Scenario	Incremental QALYs	Incremental cost	ICER (change from company's updated base case)
PD-L1 TPS<1%			
Company's base case model	[redacted]	[redacted]	**£48,742**
ERG preferred analysis	[redacted]	[redacted]	**£62,619** (+£13,877)
PD-L1 TPS 1-49%			
Company's base case model	[redacted]	[redacted]	**£28,190**
ERG preferred analysis	[redacted]	[redacted]	**£37,669** (+£9,479)
PD-L1 TPS ≥50%			
Company's base case model	[redacted]	[redacted]	**£18,398 (SWQ)**
ERG preferred analysis	[redacted]	[redacted]	**£16,097 (SWQ)** (-£2,301)

ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year; PD-L1 - programmed death ligand 1; TPS - tumour proportion score; SWQ – South-West quadrant

The ERG's full critique of the company's economic analyses and the ERG's exploratory analyses can be found in the main ERG report (Sections 4.4 and 4.5, respectively).

2. BACKGROUND

2.1 Introduction

This Evidence Review Group (ERG) report presents a summary and critique of the company's submission[1] relating to the Cancer Drugs Fund (CDF) guidance review of pembrolizumab in combination with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (NSCLC).

2.2 Current NICE recommendation

In September 2019, the National Institute for Health and Care Excellence (NICE) published its final guidance on the use of pembrolizumab in combination with carboplatin and paclitaxel for untreated metastatic squamous NSCLC.[2] The final NICE guidance for TA600 makes the following recommendation: *"Pembrolizumab, with carboplatin and paclitaxel, is recommended for use within the Cancer Drugs Fund as an option for untreated metastatic squamous non-small-cell lung cancer (NSCLC) in adults only if: pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier if disease progresses, and the company provides pembrolizumab according to the managed access agreement"* (NICE Technology Appraisal Guidance Number 600 [TA600][2]).

The key clinical evidence which informed TA600 came from KEYNOTE-407: a Phase III, multi-centre, triple-blind, randomised controlled trial (RCT) which assessed the efficacy and safety of pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel (pembrolizumab combination therapy) versus placebo plus carboplatin and paclitaxel/nab-paclitaxel (control).[3] At the time of the original appraisal, the clinical data related to Interim Analysis 2 (IA2) of KEYNOTE-407 (data cut-off April 2018). The data from IA2 were immature: the median duration of follow-up at IA2 was reported to be 7.8 months (range 0.1 to 19.1 months) and only 205 (36.7%) death events had occurred (85 [30.6%] events in the pembrolizumab combination therapy group and 120 [42.7%] events in the control group).[4]

During TA600, the Appraisal Committee considered that the most plausible incremental cost-effectiveness ratio (ICER), including commercial arrangements for pembrolizumab and subsequent treatments, was above £50,000 per quality-adjusted life year (QALY) gained. However, the Appraisal Committee considered this estimate to be highly uncertain, in particular due to the short duration of follow-up at IA2 of KEYNOTE-407 and concerns that subsequent treatment benefits in the standard care group were not fully reflected in the company's health economic model.[2] The final NICE guidance for TA600 also noted that the considerable uncertainty regarding the expected overall survival (OS) in the standard care group resulted in uncertainty regarding whether NICE's End-of-Life (EoL) criteria were met. After taking into account model-based estimates of survival as well as expert clinical opinion, the Appraisal Committee concluded that, on balance, NICE's EoL criteria may be met.

In light of the uncertainty surrounding the immature data from IA2 of KEYNOTE-407, the Appraisal Committee agreed that:

- Further data on OS would inform decisions on the effectiveness of pembrolizumab combination therapy versus standard care, both within the intention-to-treat (ITT) population and the programmed death ligand 1 (PD-L1) tumour proportion score (TPS) subgroups (defined as TPS <1%, 1-49% and ≥50%);
- Further data on OS in the standard care group, particularly relating to subsequent immunotherapy benefits, would inform decisions about whether NICE's EoL criteria have been met.[2]

The Appraisal Committee subsequently recommended pembrolizumab combination therapy for use within the Cancer Drugs Fund (CDF), conditional on the company adhering to the conditions set out in the managed access agreement.

In February 2020, the company submitted additional evidence for this CDF guidance review based on the final analysis of KEYNOTE-407 (data cut-off May 2019). The final data analysis provides an additional [redacted] months of follow-up compared with IA2. These updated clinical data, and their use within the company's health economic model used in TA600, are summarised and critiqued within this ERG report.

2.3 Terms of engagement for CDF review

The terms of engagement for the CDF guidance review[5] are reproduced in Table 4. The contents of the NICE terms of engagement document are not binding, but provide context for NICE and the company in their preparation for the CDF review.

Table 4: Terms of engagement for CDF guidance review

Area	Committee discussion and preferred assumptions
Population	• Adults with untreated, metastatic, squamous non-small-cell lung cancer (NSCLC)
Comparators	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab monotherapy (only in PD-L1-positive NSCLC if the tumour expresses at least a 50% TPS)
Comparative evidence	• KEYNOTE-407[3] compares pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel with placebo plus carboplatin and paclitaxel or nab-paclitaxel in adults with untreated advanced or metastatic squamous NSCLC with an ECOG performance status of 0 or 1 • The committee concluded all standard chemotherapy treatments can be considered to be of equal efficacy, and therefore KEYNOTE-407 was relevant for decision-making for this population • The company performed an indirect treatment comparison to compare pembrolizumab combination with pembrolizumab monotherapy for people whose tumours express PD-L1 with at least a 50% TPS o Median OS was not reached for the PD-L1 tumour proportion score of 50% or higher subgroup in either arm of KEYNOTE-407 o The HR for the comparison was 0.97 (95% CI 0.50 to 1.89) o The committee concluded that the outputs from the indirect treatment comparison were not robust enough for decision-making • The subgroup analysis of those with a TPS of lower than 50% is not robust enough for decision-making o The same extrapolation method as the ITT population was applied to estimate OS for the PD-L1 subgroups. These extrapolations may not be the most appropriate for subgroup analyses o In addition, the ERG's clinical advisers could not give survival estimates by PD-L1 TPS because it was too uncertain
Model structure	• The company's model structure is appropriate for decision-making
Stopping rule	• 2-year stopping rule is appropriate given current available evidence but should be reviewed in light of new evidence
Extrapolation of overall survival	• Modelling using the SEER database[6] is not appropriate for decision-making because it does not include second-line immunotherapy treatments • A log-logistic model with no cut-point for both treatment arms, is more appropriate for decision-making when considering the overall population • It is currently unclear what extrapolation is most appropriate for any subgroup analyses, as evidence presented to committee was not robust enough for decision-making
Subsequent treatment	• 50% of people in the standard care arm would be offered subsequent treatments (of these, 75% would have atezolizumab and 25% would have pembrolizumab)
Utilities	• Preference to use progression-based approach: pre-progression utility value from KEYNOTE-407 and a post-progression value (0.58) from the TOPICAL trial (Khan *et al*, 2014[7])
Duration of treatment effect	• Lifetime treatment effect for pembrolizumab combination therapy was not considered to be plausible because there was no evidence to suggest this duration of benefit:

Area	Committee discussion and preferred assumptions
	○ The ERG log-logistic model did not include an explicit treatment effect but did include a varying HR over time because the parametric extrapolations were chosen to match their clinical adviser estimates
End of life	• The committee noted that its preferred ERG model estimates that, for the overall population (that is, irrespective of PD-L1 status), people currently live for on average 2.17 years on chemotherapy. This exceeds the normal maximum that is considered a short life expectancy (24 months) • The committee considered that those with TPS ≥50% may live for longer than that estimated by the model as they would be able to take pembrolizumab monotherapy. However, the committee used the overall population for decision-making because the evidence for this subgroup was unsuitable • The committee heard from the clinical experts that the EoL criteria had been met for non-squamous NSCLC in previous appraisals, and that squamous NSCLC tends to have a poorer prognosis • Based on the current comparative evidence presented, the committee concluded pembrolizumab with carboplatin and paclitaxel might meet the EoL criteria • The committee noted that because the interim trial data were of very short duration, the modelled estimates were based on very immature data. It considered it was plausible that further evidence presented at the end of the data collection period, specifically the comparator arm of KEYNOTE-407, would provide more reliable evidence on whether those with untreated metastatic squamous NSCLC (or subgroups within that population) had a life expectancy of less than 24 months

ECOG - European Cooperative Oncology Group; TPS - tumour proportion score; OS - overall survival; PD-L1 - programmed death-ligand 1; CI - confidence interval; HR - hazard ratio; SEER - Surveillance Epidemiology and End Results; ERG - Evidence Review Group; ITT - intention-to-treat; NSCLC - non-small-cell lung cancer; EoL - End-of-Life

2.4 Evidence submitted by the company

The company's CDF submission includes the following items:

- A main CDF company submission document[1] (hereafter referred to as the "CDF-CS")
- A document containing appendices to the CDF-CS.[8] This includes:
  - The Summary of Product Characteristics (SmPC) and Patient Information Leaflet for pembrolizumab (CDF-CS, Appendix 1)
  - Progression-free survival (PFS) results from KEYNOTE-407 based on investigators' assessments (CDF-CS, Appendix 2)
  - Clinical subgroup analyses from KEYNOTE-407 (CDF-CS, Appendix 3)
  - Model results for each PD-L1 subgroup (TPS <1%, 1-49% and ≥50%; CDF-CS, Appendix 4)
- An executable model used to generate the results presented in the CDF-CS and its appendices.

In addition, the company provided responses to clarification questions raised by the ERG.[9]

2.5 Managed access agreement and comparator Patient Access Scheme

At the time of entry into the CDF, the managed entry agreement included a Patient Access Scheme (PAS) which took the form of a simple price discount of [redacted]. At the time of writing, this PAS remains in place. A comparator PAS (cPAS) is also in place for atezolizumab, which is included as a subsequent-line therapy in the company's model; the results of the economic analyses undertaken by the company and the ERG including this cPAS are provided as a confidential appendix to this report.

3. CLINICAL EFFECTIVENESS

This section provides a summary and critique of the evidence reported in the CDF-CS.[1]

3.1 Summary of clinical effectiveness evidence presented

3.1.1 Overall survival

Figure 1 presents a Kaplan-Meier plot of OS within the ITT population based on the final data-cut of KEYNOTE-407. Median OS and hazard ratios (HRs) for the ITT population and by PD-L1 TPS subgroup are summarised in Table 5.

Based on the final data-cut of KEYNOTE-407, 365 deaths (65.3%) had been reported: 168 (60.4%) deaths were reported in the pembrolizumab combination therapy group and 197 (70.1%) deaths were reported in the control group. Within the ITT population, median OS was 5.5 months longer in the pembrolizumab combination therapy group compared with the control group (17.1 months versus 11.6 months). The HR for OS was 0.71 (95% confidence interval (CI): 0.58, 0.88; *p*=[redacted]) in favour of pembrolizumab combination therapy. A statistically significant OS advantage was reported for pembrolizumab combination therapy within the PD-L1 TPS 1-49% subgroup (HR=0.59, 95% CI 0.42, 0.84; *p*=[redacted]). The HRs for OS within the TPS <1% and ≥50% subgroups were 0.79 in both subgroups; these were not statistically significant (*p*=[redacted] and *p*=[redacted], respectively).[1]

Figure 1: Kaplan-Meier plot of overall survival, ITT population, KEYNOTE-407 final 2019 data-cut (reproduced from CDF-CS, Figure 1)

[redacted]

Table 5: Summary of overall survival results, ITT population and PD-L1 subgroups, KEYNOTE-407 final 2019 data-cut

Population	N	Number of events	Median, months (95% CI)	HR, intervention vs. control (95% CI)
ITT population				
Pembrolizumab combination	278	168	17.1 (14.4, 19.9)	0.71 (0.58, 0.88)
Control	281	197	11.6 (10.1, 13.7)	[redacted]
PD-L1 TPS <1% subgroup				
Pembrolizumab combination	95	[redacted]	[redacted]	0.79 (0.56, 1.11)
Control	99	[redacted]	[redacted]	[redacted]
PD-L1 TPS 1-49% subgroup				
Pembrolizumab combination	103	[redacted]	[redacted]	0.59 (0.42, 0.84)
Control	104	[redacted]	[redacted]	[redacted]
PD-L1 TPS ≥50% subgroup				
Pembrolizumab combination	73	[redacted]	[redacted]	0.79 [redacted]
Control	73	[redacted]	[redacted]	[redacted]

N - number; ITT - intention-to-treat; PD-L1 - programmed death ligand 1; TPS - tumour proportion score; HR - hazard ratio; NE – not evaluable

3.1.2 Progression-free survival

Figure 2 presents a Kaplan-Meier plot of progression-free survival (PFS) based on blinded independent central review (BICR) within the ITT population based on the final data-cut of KEYNOTE-407. Median PFS and HRs for the ITT population and by PD-L1 TPS subgroup are summarised in Table 6.

Based on the final data-cut of KEYNOTE-407, 469 PFS events (83.9%) had been reported: 217 (78.1%) PFS events were reported in the pembrolizumab combination group and 252 (89.7%) PFS events were reported in the control group. Within the ITT population, median PFS was 2.9 months longer in the pembrolizumab combination group compared with the control group (8.0 months versus 5.1 months). The HR for PFS was 0.57 (95% CI: 0.47, 0.69; $p<$[redacted]) in favour of pembrolizumab combination therapy. A statistically significant PFS advantage was reported for pembrolizumab combination therapy within all three PD-L1 subgroups; the HRs for the TPS<1%, TPS 1-49% and TPS≥50% subgroups were reported to be 0.67, 0.52 and 0.43, respectively; $p<$[redacted] for all).[1]

Figure 2: Kaplan-Meier plot of progression-free survival, ITT population, BICR assessment using RECIST 1.1, KEYNOTE-407 final 2019 data-cut (reproduced from CDF-CS, Figure 6)

Table 6: Summary of progression-free survival results, ITT population and PD-L1 subgroups, KEYNOTE-407 final 2019 data-cut

Population	N	Number of events	Median, months (95% CI)	HR, intervention vs. control (95% CI)
ITT population				
Pembrolizumab combination	278	217	8.0 (6.3, 8.4)	0.57 (0.47, 0.69)
Control	281	252	5.1 (4.3, 6.0)	[redacted]
PD-L1 TPS <1% subgroup				
Pembrolizumab combination	95	[redacted]	[redacted]	0.67 (0.49, 0.91)
Control	99	[redacted]	[redacted]	[redacted]
PD-L1 TPS 1-49% subgroup				
Pembrolizumab combination	103	[redacted]	[redacted]	0.52 (0.38, 0.71)
Control	104	[redacted]	[redacted]	[redacted]
PD-L1 TPS ≥50% subgroup				
Pembrolizumab combination	73	[redacted]	[redacted]	0.43 (0.29, 0.63)
Control	73	[redacted]	[redacted]	[redacted]

N - number; ITT - intention-to-treat; PD-L1 - programmed death ligand 1; TPS - tumour proportion score; HR - hazard ratio

3.1.3 Other outcomes presented in the CDF-CS

Sections A.6.5 and A6.6.6 of the CDF-CS[1] also present updated information relating to the duration of exposure to study treatments and the proportions of patients receiving subsequent therapies together with information about their duration. These are not of central interest to the clinical review and are not

reproduced here. Updated information regarding the use of subsequent-line therapies is included in the company's updated model; this is discussed in Section 4.2.5.

3.1.4 Adverse events

The CDF-CS[1] does not provide any further adverse event (AE) data from the final data-cut of KEYNOTE-407. The terms of reference document for the CDF review does not include a requirement for providing additional AE data from the trial.

3.2 ERG critique of the updated clinical evidence from the final data-cut of KEYNOTE-407

3.2.1 Overall survival

The ERG notes that the OS data from the final data-cut of KEYNOTE-407 are considerably more mature than those from IA2. At the final data-cut off, the median duration of follow-up was 14.3 months, compared with 7.8 months at IA2. During the interval between IA2 and the final analysis of KEYNOTE-407, there were an additional 83 deaths in the pembrolizumab combination therapy group and an additional 77 deaths in the combination therapy group. The HR for OS within the ITT population based on the final analysis is less favourable than the HR based on IA2 (HR from final analysis = 0.71, 95% CI 0.58, 0.88; [redacted] versus HR from IA2 = 0.64, 95% CI 0.49, 0.85; p=0.0008). The OS advantage for pembrolizumab combination therapy remains statistically significant in the final analysis.

The updated Kaplan-Meier plot for the ITT population shows a clearer prolonged separation of the OS functions between the treatment groups compared with previous data-cut (see Figure 1 and company's original submission,[10] Figure 4). However, there remains uncertainty surrounding the long-term treatment effect of pembrolizumab combination therapy on OS, as few patients remain at risk beyond the maximum treatment duration of 35 cycles ([redacted] pembrolizumab group patients at risk at month 25, see Figure 1).

3.2.2 Progression-free survival

As with OS, the final data-cut of KEYNOTE-407 also provides more mature PFS data compared with IA2. During the interval between IA2 and the final analysis of KEYNOTE-407, there were an additional 65 PFS events in the pembrolizumab combination therapy group and an additional 55 PFS events in the control group. The HR for PFS within the ITT population from the final analysis is very similar to that estimated from IA2 (HR from final analysis = 0.57; 95% CI 0.47, 0.69; p[redacted] versus HR from IA2 = 0.56, 95% CI: 0.45, 0.70; p<0.0001). The PFS advantage for pembrolizumab combination therapy remains statistically significant in the final data-cut.

As with OS, there remains uncertainty regarding the long-term treatment effect of pembrolizumab combination therapy on PFS, as few patients remain at risk after discontinuation of pembrolizumab after 35 cycles of treatment ([redacted] pembrolizumab group patients at risk at month 25, see Figure 2).

3.2.3 Adverse events

The ERG believes that longer-term data on AEs from KEYNOTE-407 would provide a more complete understanding of the toxicity profile for pembrolizumab combination therapy. However, this was not a requirement set out in the CDF terms of reference document and no additional AE data are provided within the CDF-CS.[1] The company's updated economic model (see Section 4) includes costs associated with AEs as reported at IA2.

During TA600, the ERG highlighted the lack of complete data on the safety profile of pembrolizumab combination therapy; this was a consequence of the following limitations in the company's original submission:[10]

- AE data collection was limited to 30 days (90 days for serious adverse events [SAEs]) after the last dose of study treatment within KEYNOTE-407
- Exclusion of non-randomised evidence or meta-analyses for AEs in pembrolizumab combination therapy in the company's systematic literature review
- Lack a network meta-analysis (NMA) for AE outcomes.[4]

These issues limited the completeness of the evidence describing the toxicity profile for patients undergoing immunotherapy in combination with standard chemotherapy. Pembrolizumab combination therapy involves toleration of the side effect profile of not only platinum combination chemotherapy, which features considerable side-effects in itself, but also immunotherapy in the form of pembrolizumab. The mechanism of action and associated toxicity profile of pembrolizumab is different to chemotherapy and therefore patients in the target population will accumulate the burden of both of these different AE profiles. As an immunotherapy, pembrolizumab can cause immune-related adverse events (irAEs) which can be severe or life-threatening; these can occur even after treatment has terminated. As well as discontinuation of therapy, which was noted in TA600 to be higher in the intervention group than the control group in KEYNOTE-407, some patients will require cessation of treatment and systemic steroids at some point during their treatment to manage irAEs; the long-term implications of such treatment interruptions are currently uncertain.

In addition, in TA600, the clinical advisors to the ERG highlighted the lack of a pembrolizumab monotherapy comparator arm in KEYNOTE-407 for patients with strong PD-L1 expression (TPS ≥50%), as is used in current clinical practice in England. This led to the clinical advisors expressing

uncertainty regarding whether pembrolizumab should be given as first-line combination therapy or whether it should be reserved for use as monotherapy for patients with PD-L1 TPS ≥50%, particularly considering this combined toxicity profile in a patient group with low life expectancy.

[redacted]

Overall, the long-term toxicity profile for pembrolizumab combination therapy remains uncertain.

4. COST-EFFECTIVENESS

This section presents a summary and critique of the company's updated model for the CDF review. Sections 4.1 and 4.2 describe the company's amendments to the model developed to inform TA600 to include the final data-cut from KEYNOTE-407. Section 4.3 presents the results of the company's updated model. Section 4.4 presents a critique of the company's new analyses. Section 4.5 presents the methods and results of additional exploratory analyses undertaken by the ERG.

4.1 Summary of company's updated economic analyses

The starting point for company's updated economic analysis is the model amended by the ERG in order to perform "ERG's pessimistic analysis 6b" in TA600 (see ERG report,[4] pages 126 to 128). The key features of the company's original model from TA600, the ERG's pessimistic analysis 6b and the company's updated CDF review model are summarised in Table 7. The company's updated model includes the following amendments (relative to ERG pessimistic analysis 6b):

- Overall survival (OS) – log-logistic models were fitted to the final data-cut of KEYNOTE-407 (no cut-point, models fitted independently to data for each treatment group)
- Progression-free survival (PFS) – hybrid approach using Kaplan-Meier estimates followed by log-normal models fitted to the final data-cut of KEYNOTE-407 (26-week cut-point, models fitted independently to data for each treatment group)
- Time to treatment discontinuation (TTD) – a generalised gamma model was fitted to the final data-cut of KEYNOTE-407 for pembrolizumab (truncated after a maximum treatment duration of 35 cycles); observed Kaplan-Meier estimates were updated for standard care group
- Subsequent treatments - probabilities of receiving second-line treatments were updated using the final data-cut of KEYNOTE-407; the durations of second-line atezolizumab and pembrolizumab in the standard care group were based on the OAK trial[11] and the KEYNOTE-010 trial,[12] respectively (previously based on KEYNOTE-407)
- Health-related quality of life – health utilities were defined according to the model health states. The utility value for the progression-free state was based on KEYNOTE-407; the utility value for the post-progression state was based on the TOPICAL trial (Khan *et al*[7]) with adjustment for the proportion of patients receiving second-line immunotherapy (consistent with ERG pessimistic analysis 6b)
- Indirect comparison in the TPS ≥50% subgroup – time-varying HRs were derived from KEYNOTE-407 and KEYNOTE-042,[13] with statistical adjustment for imbalances in second-line immunotherapy use in the chemotherapy arms of each trial.

Overall, these amendments are in line with the terms of engagement for the CDF guidance review (see Table 4). The company's model amendments are described in detail in Section 4.2.

Table 7: Summary of company's updated model

Model feature	Company's original model (TA600)[10]	ERG pessimistic analysis 6b (TA600)[4]	Company's updated model (CDF review)[1]	ERG comments
Model type	Survival model with utilities defined by time to death and costs independent of progression status (PFS models fitted but not used)	Partitioned survival model with utilities and costs based on progression status	Partitioned survival model with utilities and costs based on progression status	Company's updated model is in line with ERG pessimistic analysis 6b
KEYNOTE-407 data-cut	IA2 (April 2018)	IA2 (April 2018)	Final (May 2019)	-
PFS – pembrolizumab combination therapy	Hybrid model - KM used up to week 26 followed by log-normal model fitted to post-26 week PFS data from KEYNOTE-407	Hybrid model - KM used up to week 26 followed by log-normal model fitted to post-26 week PFS data from KEYNOTE-407	Hybrid model - KM used up to week 26 followed by log-normal model fitted to post-26 week PFS data from KEYNOTE-407	Company's updated model is in line with ERG pessimistic analysis 6b. PFS models fitted to final data-cut.
PFS – standard care	Hybrid model - KM used up to week 26 followed by log-normal model fitted to post-26 week PFS data from KEYNOTE-407	Hybrid model - KM used up to week 26 followed by log-normal model fitted to post-26 week PFS data from KEYNOTE-407	Hybrid model - KM used up to week 26 followed by log-normal model fitted to post-26 week PFS data from KEYNOTE-407	
OS – pembrolizumab combination therapy	Hybrid model - KM used up to week 52 of KEYNOTE-407, followed by mortality data from SEER with RR for death derived from months 7-12 of KEYNOTE-407. Constant mortality rate assumed beyond 13 years.	Log-logistic model fitted to KEYNOTE-407 OS data (no cut-point)	Log-logistic model fitted to KEYNOTE-407 OS data (no cut-point)	Company's updated model is in line with ERG pessimistic analysis 6b. OS models fitted to final data-cut.
OS – standard care	Hybrid model - KM used up to week 52 of KEYNOTE-407, followed by mortality data from SEER	Log-logistic model fitted to KEYNOTE-407 OS data (no cut-point)	Log-logistic model fitted to KEYNOTE-407 OS data (no cut-point)	

Model feature	Company's original model (TA600)[10]	ERG pessimistic analysis 6b (TA600)[4]	Company's updated model (CDF review)[1]	ERG comments
TTD – pembrolizumab combination therapy	Generalised gamma fitted to KEYNOTE-407 TTD data (truncated at 35 cycles)	Generalised gamma fitted to KEYNOTE-407 TTD data (truncated at 35 cycles)	Generalised gamma fitted to KEYNOTE-407 TTD data (truncated at 35 cycles) for ITT population and PD-L1 TPS <1% and TPS 1-49% subgroups. Weibull model applied to TPD ≥50% subgroup.	Company's updated model is generally in line with ERG pessimistic analysis 6b. TTD models fitted to final data-cut. The original CS applied an exponential model for TTD in the PD-L1 TPS ≥50% subgroup.
TTD – standard care	Observed KM estimates from KEYNOTE-407	Observed KM estimates from KEYNOTE-407	Observed KM estimates from KEYNOTE-407	Company's updated model is in line with ERG pessimistic analysis 6b. KM function updated using final data-cut
Utility approach	Time to death utilities estimated according to four categories based on KEYNOTE-407 data	Utilities defined according to progression status. Progression-free utility derived from KEYNOTE-047. Post-progression utility taken from Khan *et al*.	Utilities defined according to progression status. Progression-free utility derived from KEYNOTE-047. Post-progression utility taken from Khan *et al*.	Company's updated model is in line with ERG pessimistic analysis 6b. Post-progression utilities adjusted according to proportion of patients receiving 2nd line immunotherapy.
Stopping rule	Pembrolizumab costs applied up to 35 cycles	Pembrolizumab costs applied up to 35 cycles	Pembrolizumab costs applied up to 35 cycles	Company's model is in line with ERG pessimistic analysis 6b.
Duration of treatment effect	No treatment effect waning assumed	No treatment effect waning assumed	Treatment effect waning assumed at 5 years for OS	Waning has little impact on the ICER for pembrolizumab combination therapy. Waning not applied to PFS (except in the PD-L1 TPS ≥50% subgroup).

Model feature	Company's original model (TA600)[10]	ERG pessimistic analysis 6b (TA600)[4]	Company's updated model (CDF review)[1]	ERG comments
Subsequent treatments	Usage and duration of subsequent treatments based on KEYNOTE-407	Usage and duration of subsequent treatments based on KEYNOTE-407	Usage and duration of subsequent treatments based on KEYNOTE-407, plus OAK, KEYNOTE-010, and KEYNOTE-024 trials and assumptions	Company's model is in line with ERG pessimistic analysis 6b. Alternative sources for subsequent treatment durations of immunotherapies applied to account for underestimation due to censoring within the KEYNOTE-407 data
Subgroup analyses	Cost-effectiveness evaluated within three PD-L1 subgroups: • TPS <1% • TPS 1-49% • TPS ≥50%	Cost-effectiveness evaluated within three PD-L1 subgroups: • TPS <1% • TPS 1-49% • TPS ≥50%	Cost-effectiveness evaluated within three PD-L1 subgroups: • TPS <1% • TPS 1-49% • TPS ≥50%	Company's model is in line with ERG pessimistic analysis 6b.
Indirect comparison for TPS ≥50% subgroup	Constant HR	Constant HR	Time-varying HR including OS adjusted for treatment switching	Time-varying HRs presented in original CS but not included in company's base case analysis in TA600. This analysis has been updated within the CDF-CS

CDF - Cancer Drugs Fund; IA2 - Interim Analysis 2; KM - Kaplan-Meier; SEER - Surveillance, Epidemiology and End Results; PD-L1 - programmed death ligand 1; TPS - tumour proportion score; HR - hazard ratio; RR - relative risk; OS - overall survival; PFS - progression-free survival; TTD - time to treatment discontinuation; CS - company's submission

4.2 Detailed description of model amendments included in company's updated model

4.2.1 Overall survival

The company's updated analyses of OS are presented in CDF-CS[1] Section A.8.1 (pages 66 to 74). The company fitted standard parametric models to the final data-cut of KEYNOTE-407. The company assessed the appropriateness of the proportional hazards assumption using several methods including examination of cumulative hazard plots and log cumulative hazard plots; however, the company subsequently fitted independent models to the available data for each trial arm. In line with ERG pessimistic analysis 6b,[4] survival models were fitted to the whole OS dataset (without cut-points). Models included the exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma distributions. Model selection was based on the examination of relative goodness-of-fit statistics (the Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) and consideration of clinical plausibility, based on expected survival estimates provided by clinical advisors to the ERG and NICE during TA600.[4, 14]

Figure 3 and

Figure 4 present Kaplan-Meier plots for OS and cumulative OS probabilities derived from the company's parametric survival models fitted to the final data-cut of KEYNOTE-407, for the pembrolizumab combination therapy and standard care groups, respectively. Table 8 summarises the AIC and BIC statistics for the company's updated OS models. Table 9 presents a comparison of estimated OS from the company's updated model, which also includes a general population mortality constraint, together with OS estimates provided by clinical advisors to the ERG and NICE during TA600.

The CDF-CS[1] notes that within the pembrolizumab combination therapy group, the Weibull distribution had the lowest AIC, whilst the exponential distribution had the lowest BIC. Within the standard care group, the log-logistic distribution had the lowest AIC, whilst the exponential distribution had the lowest BIC (see Table 8). The company selected the log-logistic model for both treatment groups on the basis that: (a) the AIC and BIC statistics for this distribution were similar to the best-fitting model, and; (b) the 5- and 10-year OS estimated predicted by this model were considered clinically plausible, based on the OS estimates provided by clinical advisors to the ERG and NICE (see Table 9).

Figure 3: Kaplan-Meier plot of OS and company's updated parametric OS models, ITT population, KEYNOTE-407 final 2019 data-cut, pembrolizumab combination therapy (generated by the ERG)

Note - OS models presented in the figure exclude the general population mortality constraint

Figure 4: Kaplan-Meier plot of OS and company's updated parametric OS models, ITT population, KEYNOTE-407 final 2019 data-cut, standard care (generated by the ERG)

Note - OS models presented in the figure exclude the general population mortality constraint

Table 8: AIC and BIC statistics, OS, ITT population, both treatment groups (reproduced from CDF-CS, Table 28)

OS model	Pembrolizumab combination therapy		Standard care	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Note - lowest AIC and BIC values highlighted in bold

Table 9: Estimated OS probabilities at 5-, 10- and 20-years (generated by the ERG)

Source of OS estimate	5 year OS	10 year OS	20 year OS
Pembrolizumab combination therapy			
KEYNOTE-407 (final data-cut)	N/a	N/a	N/a
Company's updated CDF model	[redacted]	[redacted]	[redacted]
ERG clinical advisors 1&2	0.20	0.11	N/a
ERG clinical advisor 3	0.15-0.20	0.05-0.10	<0.02
NICE clinical advisor	0.18	0.11	0.04
Standard care			
KEYNOTE-407 (final data-cut)	N/a	N/a	N/a
Company's updated CDF model	[redacted]	[redacted]	[redacted]
ERG clinical advisors 1&2	0.08	0.03	N/a
ERG clinical advisor 3	0.08-0.10	0.05	N/a
NICE clinical advisor	0.09	0.03	0.00

OS - overall survival; CDF - Cancer Drugs Fund; ERG - Evidence Review Group; NICE - National Institute for Health and Care Excellence; N/a - not applicable

4.2.2 Progression-free survival

The company's updated analyses of PFS are presented in CDF-CS[1] Section A.8.2 (pages 74 to 81). The company's updated analysis of PFS was similar to that for OS. However, for this endpoint the company used a hybrid approach based on the updated observed Kaplan-Meier PFS estimates up to week 26 of KEYNOTE-407, followed by estimates derived from parametric survival models fitted to post-week 26 data for all subsequent timepoints. As with OS, separate models were fitted independently to the available data for each trial arm. Models included the exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma distributions.

Figure 5 and Figure 6 present Kaplan-Meier plots for PFS and cumulative PFS probabilities derived from the company's parametric survival models fitted to the final data-cut of KEYNOTE-407, for the pembrolizumab combination therapy and standard care groups, respectively. Table 10 summarises the AIC and BIC statistics for the company's fitted PFS models. Table 11 presents a comparison of estimated PFS from the company's updated model, which includes a constraint to ensure that PFS never

exceeds OS, together with PFS estimates provided by clinical advisors to the ERG and NICE during TA600.[4, 14]

The CDF-CS[1] states that the log-normal model was selected to represent PFS for both treatment groups as it had the lowest AIC and BIC. The CDF-CS does not discuss whether the clinical plausibility of alternative parametric models for PFS was considered.

Figure 5: Kaplan-Meier plot of PFS and company's updated parametric PFS models (26-week cut-point), ITT population, KEYNOTE-407 final 2019 data-cut, pembrolizumab combination therapy (generated by the ERG)

KM - Kaplan-Meier
Note - PFS models presented in the figure exclude the general population mortality constraint

Figure 6: Kaplan-Meier plot of PFS and company's updated parametric PFS models (26-week cut-point), ITT population, KEYNOTE-407 final 2019 data-cut, standard care (generated by the ERG)

KM - Kaplan-Meier
Note - PFS models presented in the figure exclude the general population mortality constraint

Table 10: AIC and BIC statistics, PFS (26-week cut-point), ITT population, KEYNOTE-407 final 2019 data-cut, both treatment groups (reproduced from CDF-CS, Table 31)

PFS model	Pembrolizumab combination therapy		Standard care	
	AIC	BIC	AIC	BIC
Exponential				
Weibull				
Log-normal				
Log-logistic				
Gompertz				
Generalised gamma				

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Note - lowest AIC and BIC values highlighted in bold

Table 11: Estimated PFS probabilities at 5-, 10- and 20-years (generated by the ERG)

Source of PFS estimate	5 year PFS	10 year PFS	20 year PFS
Pembrolizumab combination therapy			
KEYNOTE-407 (final data-cut)	N/a	N/a	N/a
Company's updated CDF model	[redacted]	[redacted]	[redacted]
ERG clinical advisors 1&2 (TA600)	0.10	N/a	N/a
ERG clinical advisor 3 (TA600)	0.10	N/a	N/a
NICE clinical advisor (TA600)	0.10	0.05	0.04
Standard care			
KEYNOTE-407 (final data-cut)	N/a	N/a	N/a
Company's updated CDF model	[redacted]	[redacted]	[redacted]
ERG clinical advisors 1&2 (TA600)	0.03	N/a	N/a
ERG clinical advisor 3 (TA600)	0.03	N/a	N/a
NICE clinical advisor (TA600)	0.03	0.00	0.00

PFS - progression-free survival; CDF - Cancer Drugs Fund; ERG - Evidence Review Group; NICE - National Institute for Health and Care Excellence; N/a - not applicable

4.2.3 Time to treatment discontinuation

The company's updated analyses of TTD are presented in CDF-CS[1] Section A.8.3 (pages 82 to 84). The company fitted standard parametric survival models to the available data for TTD in the pembrolizumab combination therapy arm of KEYNOTE-407. Models included the exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma distributions. Based on the information provided in the CDF-CS, the company selected their preferred model on the basis of goodness-of-fit statistics (AIC and BIC).

Figure 7 presents Kaplan-Meier plots for TTD and cumulative TTD probabilities derived from the company's parametric models for the pembrolizumab combination therapy group based on the final data-cut of KEYNOTE-407. Table 10 summarises the AIC and BIC statistics for the company's TTD models.

The CDF-CS[1] states that the generalised gamma distribution had the lowest AIC, whilst the exponential distribution had the lowest BIC (see Table 12). The company selected the generality gamma distribution for use in the base case analysis, as the BIC for this function was similar to that of the exponential function (the best-fitting model according to this criterion). As noted in Table 7, the company's economic model assumes that TTD for the pembrolizumab combination therapy group is zero after 35 cycles of treatment to reflect the maximum treatment duration for pembrolizumab; hence, the extrapolated portion of the distribution is not used.

In line with the company's original model, TTD for the standard care group was based on observed cumulative probabilities of remaining on treatment derived from the Kaplan-Meier function; parametric models were not fitted to the available data. These probabilities were obtained from the final data-cut of KEYNOTE-407 (see Figure 8).

Figure 7: Kaplan-Meier plot of TTD and company's updated parametric TTD models, ITT population, KEYNOTE-407 final 2019 data-cut, pembrolizumab combination therapy (generated by the ERG)

TTD - time to treatment discontinuation

Table 12: AIC and BIC statistics, TTD, ITT population, KEYNOTE-407 final 2019 data-cut, pembrolizumab combination therapy (reproduced from CDF-CS, Table 32)

TTD model	Pembrolizumab combination therapy	
	AIC	BIC
Exponential		
Weibull		
Log-normal		
Log-logistic		
Gompertz		
Generalised gamma		

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
Note - lowest AIC and BIC values highlighted in bold

Figure 8: Kaplan-Meier plot of TTD, ITT population, KEYNOTE-407 final 2019 data-cut, standard care (generated by the ERG)

TTD - time to treatment discontinuation

4.2.4 Health utilities

In line with ERG pessimistic analysis 6b, the company's updated model uses health utilities defined according to the model health states (the presence/absence of disease progression). The utility value for the progression-free health state is based on IA2 of KEYNOTE-407. The utility value for the post-progression health state was taken from Khan *et al*,[7] with adjustment for the proportion of patients receiving second-line immunotherapy, based on the same assumptions as those used in ERG pessimistic analysis 6b. The company has not updated the utility estimate for the progression-free health state using the final data-cut of KEYNOTE-407. The utility values used in the company's updated model are summarised in Table 13.

Table 13: Utility values used in the model, by treatment group and health state

Health state	Pembrolizumab combination therapy	Standard care
Progression-free	[redacted]	[redacted]
Post-progression*	0.61	0.62

** Includes assumptions of additional PFS time resulting from use of second-line immunotherapy in line with assumptions included in ERG pessimistic analysis 6b*

4.2.5 Subsequent treatments

The company's model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) disease management; (iv) second-line therapy; (v) management of AEs, and; (vi) end-of-life (terminal care) costs. The company's CDF review model includes updated costs of subsequent therapy (second-line treatment) using the final data-cut of KEYNOTE-407. Second-line treatment costs are applied once-only at the point of discontinuation of first-line therapy.

Table 14 presents the company's updated estimates of the probability of receiving second-line treatments, the distribution of treatment regimens amongst those patients who receive subsequent-line treatment, and mean treatment duration. Based on the final data-cut of KEYNOTE-407, the probability of receiving subsequent treatment is [redacted] for the pembrolizumab combination therapy group and [redacted] for the standard care group. In line with ERG pessimistic analysis 6b, patients who discontinue first-line pembrolizumab treatment (as monotherapy or in combination with chemotherapy) are assumed to be ineligible for second-line immunotherapy and may instead receive standard chemotherapy only. Patients in the standard care group are assumed to receive second-line treatment with immunotherapy (75% of patients are assumed to receive atezolizumab and 25% of patients are assumed to receive pembrolizumab, therefore no patient receives subsequent chemotherapy). The ERG notes that whilst most control group patients in KEYNOTE-407 received second-line immunotherapy, a proportion of these patients received standard chemotherapy alone; this issue is discussed in further detail in Section 4.4.6. The distribution of subsequent-line chemotherapy regimens applied in the pembrolizumab combination therapy group was based on the final analysis of KEYNOTE-407, whilst the distribution for the pembrolizumab monotherapy group was based on KEYNOTE-024.

For those patients in the standard care group who go on to receive second-line immunotherapy, mean treatment duration for atezolizumab was based on estimates from NICE TA520[15] (33.9 weeks, based on the OAK trial[11]), whilst mean treatment duration for pembrolizumab was based on KEYNOTE-010 ([redacted] weeks, data-cut March 2018).[12] The CDF-CS[1] states that the final data-cut of KEYNOTE-407 was not used to estimate the mean duration of subsequent immunotherapies because: *"given right censoring observed within the KEYNOTE-407 FA [final analysis] data for the durations of these treatments in 2L, limiting the observation window and under-estimating mean durations for these regimens."* For patients receiving second-line chemotherapy within the pembrolizumab combination therapy group, the mean treatment duration was estimated from the final data-cut of KEYNOTE-407 ([redacted] weeks), whilst for pembrolizumab monotherapy the duration of second-line chemotherapy was taken from KEYNOTE-024 ([redacted] weeks).[3, 16]

Table 14: Distribution and duration of second-line treatments by treatment group, based on final data-cut of KEYNOTE-407, other immunotherapy trials and committee's preferred assumptions in TA600

Subsequent-line treatment	Pembrolizumab combination therapy	Standard care	Pembrolizumab monotherapy
Probability of receiving second-line treatment			
Probability of receiving second-line treatment	[redacted]	[redacted]	[redacted]
Probability of receiving individual regimen (conditional on receiving subsequent-line therapy)			
Atezolizumab	0.0%	75.0%*	0.0%
Pembrolizumab	0.0%	25.0%*	0.0%
Carboplatin plus gemcitabine	[redacted]	[redacted]	[redacted]
Carboplatin plus paclitaxel	[redacted]	[redacted]	[redacted]
Cisplatin plus gemcitabine	[redacted]	[redacted]	[redacted]
Cisplatin plus paclitaxel	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]
Duration of subsequent-line treatment (weeks)			
Duration of subsequent-line atezolizumab	n/a	33.9†	n/a
Duration of subsequent-line pembrolizumab	n/a	[redacted]‡	n/a
Duration of subsequent-line chemotherapy	[redacted]	n/a	[redacted]

* *Based on the committee's preferred assumptions in TA600 rather than experience of the KEYNOTE-407 trial*
† Based on the OAK trial
‡ Based on KEYNOTE-010

4.2.6 Subgroup analyses

The CDF-CS[1] presents the results of subgroup analyses according to three PD-L1 TPS groups: TPS <1%; TPS 1-49% and TPS ≥50%); this is in line with the terms of engagement for the CDF review (see Table 4). Within the PD-L1 TPS <1% and 1-49% subgroups, the model compares the cost-effectiveness of pembrolizumab combination therapy versus carboplatin plus paclitaxel using data from KEYNOTE-407. Within the TPS ≥50% subgroup, pembrolizumab combination therapy is compared against pembrolizumab monotherapy based on the company's indirect comparison of KEYNOTE-407 and KEYNOTE-042. The methods and results of this indirect comparison within the TPS ≥50% subgroup are outlined in Section 4.2.6.1. The implementation of all subgroup analyses within the company's updated model is described in Section 4.2.6.2.

4.2.6.1 Indirect comparison of pembrolizumab monotherapy versus pembrolizumab combination therapy (PD-L1 TPS ≥50% subgroup)

In order to inform the economic analysis of pembrolizumab combination therapy within the PD-L1 TPS ≥50% subgroup, the company undertook an indirect comparison of pembrolizumab monotherapy versus pembrolizumab combination therapy for PFS and OS using data from KEYNOTE-407 and KEYNOTE-042. The data and methods used to inform the indirect comparison are presented in detail in CDF-CS[1] Section A.7.1 (pages 47 to 65). Within KEYNOTE-407, [redacted] patients with squamous NSCLC with PD-L1 TPS ≥50% were included in the analysis (pembrolizumab combination therapy N=[redacted]; standard care

N=[redacted]). Within KEYNOTE-042, [redacted] patients with squamous NSCLC and PD-L1 TPS≥50% were included in the analysis (pembrolizumab monotherapy N=[redacted]; standard care N=[redacted]). Standard chemotherapy was used as a common anchor between the two trials included in the comparison.

In both trials, a proportion of patients received subsequent-line immunotherapies after discontinuation of the study drug. In order to adjust for imbalances in second-line immunotherapy use between the studies, the company used the 2-stage method without re-censoring.[17] The company used these adjusted PFS and OS data to estimate time-varying HRs for pembrolizumab monotherapy versus pembrolizumab combination therapy assuming that both PFS and OS follow the log-logistic distribution. Treatment effects were estimated using the switching-adjusted data at months 1, 3, 6 , 9, 12, 15, 18, 21 and 24. The indirect comparison between the pembrolizumab arms was performed using the method reported by Bucher *et al*.[18] The results of the company's indirect comparisons for OS and PFS are summarised in Table 15. As shown in the table, the indirect comparison suggests that pembrolizumab monotherapy is more effective than pembrolizumab combination therapy from month 6 for OS and from month 9 for PFS.

Table 15: Estimated time-varying hazard ratios for overall survival and progression-free survival, pembrolizumab monotherapy versus pembrolizumab combination therapy (assuming log-logistic distribution), PD-L1 TPS ≥50% subgroup

Month	OS			PFS		
	HR	Lower 95% CI	Upper 95% CI	HR	Lower 95% CI	Upper 95% CI
1	[redacted]					
3						
6						
9						
12						
15						
18						
21						
24						

HR - hazard ratio; CI - confidence interval; PD-L1 - programmed death ligand 1; TPS - tumour proportion score

4.2.6.2 Implementation of subgroup analyses in the company's updated model

The company's subgroup analyses are the same as the analyses for the ITT population, except that: (a) subgroup-specific parametric survival models for PFS, OS and TTD were fitted to the final data-cut of KEYNOTE-407, and; (ii) within the PD-L1 TPS ≥50% subgroup, TTD is assumed to follow a Weibull distribution. The CDF-CS[1] does not present any information relating to the criteria used to select PFS, OS or TTD models in the PD-L1 subgroups. Figure 9 and Figure 10 present the company's implemented time-varying HRs for OS and PFS within the PD-L1 TPS ≥50% subgroup, as applied in the company's updated economic model. It should be noted that the company's model assumes that from month 37,

the HRs for PFS and OS increase linearly to 1.0 by year 5. The company's model assumes that the use of subsequent-line treatment in each TPS subgroup is the same as that for the ITT population.

Table 16: Summary of survival model assumptions applied within PD-L1 subgroup analyses

Treatment group	OS	PFS	TTD
PD-L1 TPS <1% and 1-49% subgroups			
Pembrolizumab combination	Log-logistic (KEYNOTE-407 subgroup data)	Hybrid Kaplan-Meier followed by log-normal (KEYNOTE-407 subgroup data, 26 week cut-point)	Generalised gamma (KEYNOTE-407 subgroup data)
Standard care	Log-logistic (KEYNOTE-407 subgroup data)	Hybrid Kaplan-Meier followed by log-normal (KEYNOTE-407 subgroup data, 26 week cut-point)	Observed Kaplan-Meier estimates (KEYNOTE-407 subgroup data)
PD-L1 TPS ≥50% subgroup			
Pembrolizumab combination	Log-logistic (KEYNOTE-407 subgroup data)	Hybrid Kaplan-Meier followed by log-normal (KEYNOTE-407 subgroup data, 26 week cut-point)	Weibull (KEYNOTE-407 subgroup data)
Pembrolizumab monotherapy	Pembrolizumab combination arm OS (log-logistic) raised to power of time-varying HR for OS from indirect comparison (see Table 15)	Pembrolizumab combination arm PFS (hybrid Kaplan-Meier log-normal) raised to power of time-varying HR for PFS from indirect comparison (see Table 15)	Observed Kaplan-Meier estimates (KEYNOTE-042/024)*

PD-L1 - programmed death ligand 1; OS - overall survival; PFS - progression-free survival; TTD - time to treatment discontinuation; HR - hazard ratio
Note - all models are fitted to the final data-cut of KEYNOTE-407
** Precise source unclear*

Figure 9: Company's implemented time-varying hazard ratios for overall survival, pembrolizumab monotherapy versus pembrolizumab combination therapy, PD-L1 TPS ≥50% subgroup

HR – Hazard ratio; OS – overall survival

Figure 10: Company's implemented time-varying hazard ratios for progression-free survival, pembrolizumab monotherapy versus pembrolizumab combination therapy, PD-L1 TPS ≥50% subgroup

HR – Hazard ratio; OS – overall survival

4.3 Company's updated cost-effectiveness results

The results of the company's updated model are summarised in Table 17. These include the correction of reporting errors in the CDF-CS identified by the ERG within all three PD-L1 TPS subgroups (see clarification response,[9] question B11).

Table 17: Company's updated cost-effectiveness results, includes correction of errors identified by the ERG, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ITT population							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,090**
Standard care	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <1% subgroup							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£48,742**
Standard care	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS 1-49% subgroup							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,190**
Standard care	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS ≥50% subgroup							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£18,398 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ITT - intention-to-treat; PD-L1 - programmed death ligand 1; TPS - tumour proportion score; SW - South West quadrant
** Undiscounted*

Based on the deterministic version of the company's model for the ITT population, pembrolizumab combination therapy is estimated to generate an additional [redacted] QALYs at an additional cost of [redacted] compared with standard care; the corresponding ICER is estimated to be £38,090 per QALY gained. The probabilistic version of the company's model produced a similar ICER of £38,834 per QALY gained. Assuming a willingness-to-pay (WTP) threshold of £50,000 per QALY gained, the probability that pembrolizumab combination therapy generates more net benefit than standard chemotherapy is [redacted]. The company's deterministic sensitivity analyses indicate that the ICER is particularly sensitive to the utility value for the progression-free state for the pembrolizumab combination therapy group, the relative dose intensity of pembrolizumab combination therapy and the function used to represent OS for the pembrolizumab combination therapy group (see CDF-CS,[1] Figure 37).

Based on the company's model, the cost-effectiveness of pembrolizumab combination therapy differs considerably between the three PD-L1 TPS subgroups. Within the TPS <1% and the TPS 1-49% subgroups, pembrolizumab combination therapy is estimated to be more effective and more expensive than standard chemotherapy; the ICERs for pembrolizumab combination therapy versus chemotherapy within the TPS <1% and TPS 1-49% subgroups are estimated to be £48,742 and £28,190 per QALY gained, respectively. Within the TPS ≥50% subgroup, pembrolizumab combination therapy is expected to generate less health and lower costs relative to pembrolizumab monotherapy: the ICER for pembrolizumab combination therapy versus pembrolizumab monotherapy is estimated to be £18,398 saved per QALY lost.

4.4 ERG critique of company's updated health economic analyses

This section presents a critique of the company's updated health economic analyses.

4.4.1 Model verification and replication of company's updated analyses

The ERG applied the company's updated survival models, health utility estimates and resource use estimates within the version of the model used to undertake ERG pessimistic analysis 6b in TA600. The ERG was able to reproduce the results of the company's updated CDF analyses within the overall population using this version of the model.

Owing to reporting errors in the CDF-CS,[1] the ERG was not initially able to replicate the company's results for any of the PD-L1 subgroups. However, in response to a request for clarification from the ERG (see clarification response,[9] question B11), the company provided corrected results for the PD-L1 TPS subgroups and the ERG was able to replicate each of these using the original model from TA600.

The ERG has two concerns regarding the implementation of the company's updated analyses:

(i) The ERG believes that the committee's preferred assumptions about subsequent-line immunotherapy use[2] in the standard chemotherapy group, which were introduced into the model following the technical engagement process for TA600, are inconsistent with the experience of the KEYNOTE-407 trial, as they apply the costs of immunotherapy to all standard care patients who receive subsequent-line treatment, yet around [redacted] of these patients received chemotherapy alone. Whilst these assumptions may reflect current clinical practice in England, they overestimate costs for the comparator group of the model. Applying updated estimates of the distribution of subsequent-line treatments using the final data-cut of KEYNOTE-407 increases the ICER for pembrolizumab combination therapy. This issue is discussed in more detail in Section 4.4.6.

(ii) The company's updated model includes an assumption that the treatment effect of pembrolizumab combination therapy on OS is lost after 5 years (beyond this point, the hazard of OS switches to that for the comparator group). However, this assumption is not applied to treatment effects on PFS, except within the PD-L1 TPS ≥50% subgroup.

4.4.2 Overall survival

With respect to the company's updated OS models, the ERG makes the following observations:

- The ERG does not have any major concerns regarding the company's updated modelling of OS within the overall ITT population. The analyses undertaken are in line with the terms of engagement for the CDF review (see Table 4). The ERG notes that the company's updated survival analysis is limited to the consideration of standard parametric models only: the company could have explored the use of more flexible models e.g. restricted cubic splines. It is unclear whether these models would have provided more plausible estimates of OS.
- Given the limited set of OS models considered within the company's updated analysis, the ERG believes that the company's decision to apply the log-logistic model for the pembrolizumab combination therapy group within their updated base case is reasonable. The long-term OS estimates derived from this model are broadly consistent with the pessimistic estimates obtained from the ERG's clinical advisor 3 during TA600 (see Table 9). The use of the log-logistic model for the standard care group results in long-term OS probabilities which are similar to or within the ranges provided by all clinical advisors to NICE and the ERG during TA600. The ERG notes however that all of these estimates are subject to uncertainty. In addition, the ERG notes that the exponential, Weibull, Gompertz and generalised gamma functions each indicate a very low (or approximately zero) probability of 10-year survival in both treatment groups.
- Figure 11 presents a comparison of the company's original base case and the ERG's preferred pessimistic OS models in TA600 (fitted to data from IA2), together with the company's updated OS models based on the final data-cut of KEYNOTE-407. With respect to the pembrolizumab combination therapy group, the company's updated log-logistic model suggests a considerably less favourable OS projection compared with their original OS model which used data from IA2 of KEYNOTE-407 and long-term estimates from SEER. The company's updated log-logistic model also suggests lower OS compared with the equivalent model fitted to the data from IA2 of KEYNOTE-407. With respect to the standard care group, the company's updated log-logistic model fitted to the final data-cut of KEYNOTE-407 is very similar to the log-logistic model fitted to IA2 of KEYNOTE-407. Both of these models indicate a more favourable OS profile compared with the company's original OS model for the standard care group.

Figure 11: Kaplan-Meier plot of OS (KEYNOTE-407 final 2019 data-cut), ERG's preferred pessimistic OS models and company's original and updated OS models, ITT population (generated by the ERG)

KM - Kaplan-Meier; SEER - Surveillance, Epidemiology and End Results; RR - relative risk

4.4.3 Progression-free survival

With respect to the company's updated PFS models, the ERG makes the following observations:

- The ERG does not have any major concerns regarding the company's updated modelling of PFS. The analyses undertaken are in line with the terms of engagement for the CDF review (see Table 4). As with OS, the ERG believes that the company could have explored whether more flexible models e.g. restricted cubic spline models, could represent the observed data and provide plausible PFS extrapolations.
- Based on the information provided in the CDF-CS,[1] it appears that the company selected their preferred models based on goodness-of-fit statistics without consideration of the clinical plausibility. However, the ERG's clinical advisors believed that the company's original estimates were plausible and these have not changed substantially (see Figure 12).
- As discussed in the ERG report, and highlighted in Table 7, the company's original model did not use PFS probabilities to determine either health outcomes or costs; however, these are used in the ERG's pessimistic analysis 6b and the company's updated model.
- The ERG notes that the choice of PFS model has less impact on the ICER than the choice of OS model (see Section 4.5).

Figure 12: Kaplan-Meier plot of PFS (KEYNOTE-407 final 2019 data-cut), and company's original and updated PFS models, ITT population (generated by the ERG)

KM - Kaplan-Meier
Note: The ERG's preferred models also applied the company's original hybrid KM log-normal models

4.4.4 Time to treatment discontinuation

The ERG notes the following regarding the company's updated analyses of TTD:

- The ERG does not have any concerns regarding the company's approach to updating TTD for the standard care group. The TTD estimates for the standard care group are identical to those applied in their original model. The ERG believes that the use of observed Kaplan-Meier estimates within the standard care group is reasonable.
- The ERG considers the company's approach to modelling TTD for the pembrolizumab combination therapy group to be weak. The company selected the generalised gamma function on the basis that it had the lowest AIC and its BIC was similar to that for the best fitting model. However, none of the survival models appear to represent the data well. Given that the full pattern of discontinuation of pembrolizumab has been observed (see Figure 7), and extrapolation of TTD is not required in the model, the ERG believes that it would be more appropriate to use cumulative TTD probabilities from the Kaplan-Meier survivor function rather than a poorly-fitting parametric function. The impact of using the observed TTD probabilities on the ICER for pembrolizumab combination therapy is explored within the ERG's exploratory analyses using the company's updated model (see Section 4.5).

4.4.5 Health utilities

The company's updated model applies health utilities according to progression status. This is in line with the terms of engagement document for the CDF review (see Table 4). Within the model, post-progression utilities are adjusted to account for additional PFS time resulting from second-line

immunotherapy use; this is consistent with the ERG's exploratory analyses in TA600. The ERG notes that the company has not updated the utility value for the progression-free state using the final data-cut of KEYNOTE-407.

In addition, the CDF-CS[1] states that the time-to-death utility approach, which was applied in the company's original base case in TA600, was explored as a scenario analysis for the updated model. However, neither the CDF-CS nor its appendices include the results of this analysis. Despite this, the ERG believes that the state-based utility approach is more appropriate for this CDF review and the absence of this alternative analysis is not a significant weakness of the CDF-CS.

4.4.6 Subsequent treatments

The company's updated model includes a combination of evidence on the probability of receiving subsequent-line treatments from the updated data-cut of KEYNOTE-407 (and KEYNOTE-024 for pembrolizumab monotherapy in the TPS ≥50% subgroup), external information on treatment duration from the OAK trial and other KEYNOTE trials, and assumptions which are intended to reflect the Appraisal Committee's beliefs regarding use of second-line immunotherapy within the standard care group.

The ERG believes that it is appropriate to update the probabilities of receiving subsequent-line treatments using the updated data-cut of KEYNOTE-407. The ERG also believes that it is reasonable to apply information on the duration of treatment with atezolizumab from the OAK trial, as this is likely to provide a less biased estimate of treatment duration compared with KEYNOTE-407.

As discussed in Section 4.4.1, the ERG has some concerns regarding the Appraisal Committee's preferred assumptions regarding subsequent-line treatments in the standard care group. Within TA600, the company's original base case model and ERG pessimistic analysis 6b applied the distribution of second-line treatments based on IA2 of KEYNOTE-407. Following the technical engagement stage of TA600, NHS England requested additional analyses to reflect the greater use of atezolizumab compared with pembrolizumab in NHS practice. This analysis was applied by assuming that of all standard care patients who go on to receive subsequent-line therapy, 75% receive atezolizumab, whilst the remaining 25% receive pembrolizumab – none of these patients were assumed to receive subsequent-line chemotherapy. However, the ERG notes that within the final data-cut of KEYNOTE-407, a proportion of patients (around [redacted]) received chemotherapy rather than immunotherapy as a subsequent-line treatment. As such, the ERG believes that both the models applied following technical engagement in TA600 and the company's updated CDF review overestimate the costs of second-line immunotherapy in the standard care group, which in turn, underestimates the ICER for pembrolizumab combination therapy. The ERG believes that it would be more appropriate to instead assume that for those patients

who received subsequent-line immunotherapy in KEYNOTE-407, costs should be applied assuming that 75% of these patients receive atezolizumab and 25% receive pembrolizumab, whilst the costs of chemotherapy should be applied to those patients who received subsequent-line chemotherapy. This alternative costing approach is included in the ERG's preferred base case analysis (see Section 4.5).

4.4.7 Subgroup analyses

The company has applied the same base case model selections for OS and PFS in the PD-L1 TPS subgroups as those applied in the ITT population. In response to a request for clarification from the ERG (see clarification response,[9] question B9), the company stated that this approach was adopted as a consequence of the lack of evidence on the long-term OS for patients within each TPS category. The company does not appear to have sought expert opinion to support the appropriateness of this approach. However, the clinical advisors to the ERG within TA600 were also unable to provide PFS or OS estimates by PD-L1 TPS subgroup due to the absence of long-term evidence. Consequently, the ERG considers that the results of these subgroup analyses should be considered highly uncertain.

With respect to the company's methods for deriving time-varying HRs within the PD-L1 TPS ≥50% subgroup, the ERG notes the following:

- The ERG considers the company's decision to adjust for post-progression pembrolizumab use in the control arms of the studies included in the indirect comparison to be reasonable.
- In response to a request for clarification from the ERG (see clarification response,[9] question B1), the company stated that a small number of patients with PD-L1 TPS ≥50% ([redacted]) in the intervention arm of KEYNOTE-042 received a second course of pembrolizumab; no patients in the control arm of KEYNOTE-407 received a second course of pembrolizumab. The company's analysis did not adjust outcomes for patients receiving a second course of pembrolizumab, nor did they include the costs of these treatments in the economic model; the ERG believes that given the small number of patients to whom this applies, failing to adjust for this, or to include the costs of these further treatment courses, will not have a substantial impact on the ICER for pembrolizumab combination therapy.
- The company's clarification response[9] (question B3) supports the use of the 2-stage method as the majority of patients switched soon after disease progression. The analyses presented do not include re-censoring and as such may be prone to informative censoring. The ERG asked the company to present separate analyses including re-censoring in order to assess its impact; however, the company was not able to provide these analyses prior to the submission of this ERG report. It is anticipated that the company will provide additional analyses including re-censoring during the technical engagement stage of the CDF review. Additional information regarding the company's treatment switching analysis without re-censoring, including the SAS

code, details of the covariates included in the analysis and the model output, are provided in the company's clarification response[9] (question B5).

- An implicit assumption of any indirect treatment comparison is that there is a balance of treatment effect modifiers across studies comparing different pairs of treatments. Although the CDF-CS mentions an imbalance in the use of immunotherapies between KEYNOTE-042 and KEYNOTE-047, it does not discuss potential treatment effect modifiers and their potential impact on the indirect comparison.
- The company's preferred survival model is a log-logistic model and the company summarised results using time-varying HRs. During the clarification phase, the ERG pointed out that a log-logistic model is an acceleration failure time (AFT) model and HRs are not a natural scale on which to describe relative treatment effects. Furthermore, the ERG noted that the logarithm of the failure odds of a log-logistic model is linear and provides a natural scale on which to estimate relative treatment effects.
- The company's indirect comparison assumes that PFS follows a log-logistic distribution. However, the company's economic model assumes that PFS follows the empirical Kaplan-Meier function followed by a log-normal distribution. This approach is inconsistent.
- The CDF-CS does not provide any justification for using the Weibull distribution for TTD in the PD-L1 TPS ≥50% subgroup.

Based on several of the concerns described above, the ERG does not consider the indirect comparison presented in the CDF-CS to be robust. During the clarification process, the ERG requested that the company undertake a new indirect comparison using the failure odds transformation of the survival functions. The ERG also requested that the company provide some discussion of potential treatment effect modifiers (see clarification response,[9] questions B6 and B8). The company was unable to provide these new analyses within the timescales available for this ERG report; it is expected that the analyses will be provided by the company during the technical engagement stage of the CDF review.

4.5 Additional exploratory analyses undertaken by the ERG

4.5.1 Description of ERG exploratory analyses

The ERG undertook three exploratory analyses, which together form the ERG's preferred base case analysis. Additional sensitivity analyses were conducted using the ERG's preferred base case. These exploratory analyses are described below.

ERG exploratory analysis 1: TTD (pembrolizumab combination therapy group only)

As shown in Figure 7, the updated Kaplan-Meier function for TTD shows the full pattern of discontinuation up to the maximum treatment duration for pembrolizumab (35 cycles; approximately 2 years). Owing to the poor fit of the company's parametric models within the first 2 years, and because

extrapolation of the TTD function is not required, the ERG amended the company's model to use cumulative probabilities derived from the Kaplan-Meier TTD function.

ERG exploratory analysis 2: Distribution of subsequent-line treatment (pembrolizumab combination therapy and standard care groups)

The company's model was amended to include the distribution of all subsequent-line therapies received in KEYNOTE-407 together with an assumption that of those patients in the standard care group who received a subsequent-line immunotherapy, 75% receive atezolizumab and the remaining 25% receive pembrolizumab. The ERG's estimated distribution of subsequent-line therapies based on the updated data-cut is shown in Table 18. The ERG notes that these assumptions deviate from the terms of engagement for the CDF review (see Table 4); nevertheless, the ERG believes that they provide consistency with respect to capturing the health benefits associated with subsequent-line therapies in KEYNOTE-407 and the resource costs required to generate those benefits. The company's revised estimates of the duration of subsequent-line treatments and the probability of receiving any subsequent-line treatment by treatment group were not amended by the ERG.

Table 18: ERG's updated distribution of all subsequent-line therapies for pembrolizumab combination therapy and standard care groups

Subsequent-line therapy	Number		Probability	
	Pembrolizumab combination	Standard care	Pembrolizumab combination	Standard care
Number receiving any subsequent-line therapy	[redacted]	[redacted]	-	-
Number receiving subsequent-line immunotherapy	0*	[redacted]	-	
Immunotherapy				
Atezolizumab†	0	[redacted]	0.00	[redacted]
Pembrolizumab (200mg)	0	[redacted]	0.00	[redacted]
Chemotherapy				
Carboplatin+gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin+paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin+gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin+paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]

** Reflects company's original assumption in TA600.*

† Incorporates Committee's preferred assumption that of those patients who receive subsequent-line therapy, 75% receive atezolizumab and 25% receive pembrolizumab

‡ Distribution of chemotherapy regimens used in KEYNOTE-407 re-weighted to account for proportion of patients who receive immunotherapy, assuming that patients can only receive one immunotherapy course. Calculations include all subsequent lines of therapy rather than second-line only. Estimates for the pembrolizumab monotherapy group were not amended.

ERG exploratory analysis 3: Application of treatment effect waning for PFS

The assumption of treatment effect waning was applied to PFS as well as OS.

ERG exploratory analysis 4: ERG preferred base case

The ERG's preferred base case analysis includes ERG exploratory analyses 1, 2 and 3.

ERG sensitivity analysis 1: Choice of OS model

Additional sensitivity analyses were undertaken using the ERG's preferred model to explore the impact of assuming alternative parametric models for OS within the ITT population and within each PD-L1 TPS subgroup.

ERG sensitivity analysis 2: Choice of PFS model

Additional sensitivity analyses were undertaken using the ERG's preferred model to explore the impact of assuming alternative parametric models for PFS within the ITT population and within each PD-L1 TPS subgroup.

4.5.2 ERG exploratory analyses results

The results of the ERG's preferred base case analysis for the ITT population are presented in Table 19. The results are presented as individual changes relative to the company's updated base case model (ERG exploratory analyses 1, 2 and 3); all individual changes are combined in ERG exploratory analysis 4.

As shown in Table 19, the analyses indicate that the use of the observed Kaplan-Meier TTD function and the inclusion of treatment effect waning on PFS do not have a substantial impact on the ICER for the ITT population. However, applying the updated distribution of subsequent-line therapies has a more pronounced effect on the cost-effectiveness of pembrolizumab combination therapy due to reduced costs in the standard care group. The ERG's preferred analysis, which combines all three of these model amendments, results in an estimated ICER for pembrolizumab combination therapy versus standard care of £47,911 per QALY gained. The probabilistic version of the ERG's preferred base case model suggests a lower ICER of £46,997 per QALY gained.

Table 19: ERG preferred base case results, pembrolizumab combination therapy versus standard care, ITT population, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,090**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 1 – Kaplan-Meier estimates for TTD							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£39,847**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 2 – Updated distribution of subsequent-line therapies							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,240**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 3 – Inclusion of treatment effect waning for PFS							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,872**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 4 – ERG preferred analysis (ERG analysis 1 to 3 combined)							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,911**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; TTD - time to treatment discontinuation; PFS - progression-free survival
**undiscounted*

Results for the PD-L1 TPS subgroups are presented in Table 20. The ICER for pembrolizumab combination therapy versus standard care in the PD-L1 TPS <1% subgroup is estimated to be £62,619 per QALY gained, whilst in the PD-L1 TPS 1-49% subgroup the ICER is estimated to be £37,669 per QALY gained. For the PD-L1 TPS ≥50% subgroup, pembrolizumab combination therapy is expected to be less effective and less expensive than pembrolizumab monotherapy; the ICER for pembrolizumab combination therapy versus pembrolizumab monotherapy is estimated to be £16,097 saved per QALY lost.

Table 20: ERG preferred base case results, pembrolizumab combination therapy versus standard care, PD-L1 TPS subgroups

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS <1% - pembrolizumab combination therapy versus chemotherapy							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£62,619**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS 1-49% - pembrolizumab combination therapy versus chemotherapy							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£37,669**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS ≥50% - pembrolizumab combination therapy versus pembrolizumab monotherapy							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£16,097 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; TTD - time to treatment discontinuation; PFS - progression-free survival; SWQ - South-West quadrant
**undiscounted*

Table 21 and Table 22 present the results of sensitivity analyses using alternative parametric models for OS within the ITT population and the PD-L1 TPS subgroups, respectively. As shown in Table 21, the choice of OS model has a marked impact on the ICER for pembrolizumab combination therapy; the company's use of the log-logistic model for OS leads to an ICER which is at the lower end of the range. This same general trend is also evident within the PD-L1 TPS <1% and TPS 1-49% subgroups (Table 22). Within the TPS ≥50% subgroup, with the exception of the exponential function, the choice of OS model has less impact on the conclusions of the analysis; however, as noted in Section 4.4.7, the ERG does not believe that the indirect comparison presented in the CDF-CS is robust.

Table 21: ERG sensitivity analysis 1 results, impact of alternative OS models, pembrolizumab combination therapy versus standard care, ITT population, deterministic

OS model	Comparator LYGs*	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
ITT population - pembrolizumab combination therapy versus standard care					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£61,515**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£73,403**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£99,539**
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	**£47,586**
Log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£47,911**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£75,222**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ITT – intention-to-treat;
**undiscounted*

Table 22: ERG sensitivity analysis 1 results, impact of alternative OS models, pembrolizumab combination therapy versus standard care, PD-L1 TPS subgroups, deterministic

OS model	Comparator LYGs*	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
PD-L1 TPS <1% - pembrolizumab combination therapy versus chemotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£91,360**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£114,214**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£177,704**
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	**£67,577**
Log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£62,619**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£248,456**
PD-L1 TPS 1-49% - pembrolizumab combination therapy versus chemotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£49,297**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£52,472**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£49,846**
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	**£36,778**
Log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£37,669**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£46,398**
PD-L1 TPS ≥50% - pembrolizumab combination therapy versus pembrolizumab monotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£122,413**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£11,418 (SWQ)**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£11,217 (SWQ)**
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	**£16,867 (SWQ)**
Log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£16,097 (SWQ)**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£13,391 (SWQ)**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; OS - overall survival' PD-L1 - programmed death ligand 1; TPS - tumour proportion score; SWQ - South-West quadrant
**undiscounted*

Table 23 and Table 24 present the results of sensitivity analyses using alternative parametric models for PFS within the ITT population and the PD-L1 TPS subgroups, respectively. As shown in the tables, the model results are less sensitive to the choice of PFS model compared with the choice of OS model.

Table 23: ERG sensitivity analysis 2 results, impact of alternative PFS models, pembrolizumab combination therapy versus standard care, ITT population, deterministic

PFS model	Comparator survival*	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
ITT population - pembrolizumab combination therapy versus standard care					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£60,229**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£55,668**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£49,986**
Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£47,911**
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	**£48,762**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£48,931**

*LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ITT - intention-to-treat; *undiscounted*

Table 24: ERG sensitivity analysis 2 results, impact of alternative PFS models, pembrolizumab combination therapy versus standard care, PD-L1 TPS subgroups, deterministic

PFS model	Comparator survival*	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
PD-L1 TPS <1% - pembrolizumab combination therapy versus chemotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£72,197**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£68,394**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£62,212**
Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£62,619**
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	**£61,820**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£61,066**
PD-L1 TPS 1-49% - pembrolizumab combination therapy versus chemotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£45,023**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£42,745**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£36,494**
Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£37,669**
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	**£38,029**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£41,211**
PD-L1 TPS ≥50% - pembrolizumab combination therapy versus pembrolizumab monotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£8,299 (SWQ)**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£10,747 (SWQ)**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£14,752 (SWQ)**
Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£16,097 (SWQ)**
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	**£15,696 (SQW)**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£15,731 (SWQ)**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; OS - overall survival' PD-L1 - programmed death ligand 1; TPS - tumour proportion score; SWQ - South West quadrant
**undiscounted*

5. END OF LIFE

NICE EoL supplementary advice should be applied in the following circumstances and when both the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

Median survival in the control arm of KEYNOTE-407 was 11.6 months. The company's updated estimates of undiscounted life years gained for the pembrolizumab combination therapy and standard care groups are summarised in Table 21 in Section 4.5.2 (ERG sensitivity analysis 1). As shown in the table, the company's base case analysis suggests that mean survival in the standard care group is 2.26 years. The CDF-CS[1] states that clinical experts commented during the committee meeting for TA600 that life expectancy for the overall squamous NSCLC population is expected to be less than 24 months, despite the availability of pembrolizumab as second-line treatment for patients with PD-L1 TPS ≥50%. The CDF-CS also states that pembrolizumab was deemed to meet the EoL criteria within the non-squamous population; hence, it is logical that pembrolizumab should also meet these criteria within the squamous population. As shown in Table 21, all of the company's parametric models suggest that the use of pembrolizumab combination therapy leads to an OS gain of 3 months or more.

The ERG notes that the company's base case model suggests that OS in the comparator group is greater than 24 months. The survival distribution for the standard care group suggests survival probabilities at 1- and 2-years of 0.51 and 0.28, respectively, with a small proportion of patients remaining alive at 10-years (probability=0.04). Overall, the ERG is uncertain whether the first criterion is met. The ERG considers it likely that the second criterion is met, but notes that there remains uncertainty regarding the long-term OS benefit associated with pembrolizumab combination therapy.

6. DISCUSSION

The final analysis of KEYNOTE-407 suggests that pembrolizumab combination therapy produces statistically significant improvements in OS and PFS within the overall ITT population. Statistically significant improvements in PFS were reported for all PD-L1 TPS subgroups; however, significant improvements in OS were only reported for the TPS 1-49% subgroup. The CDF-CS does not include any additional information on AEs from the final data-cut of KEYNOTE-407; as such, the long-term toxicity profile of pembrolizumab combination therapy, particularly with respect to irAEs, remains uncertain.

The ERG's preferred base case analysis suggests that the ICER for pembrolizumab combination therapy versus standard care in the overall ITT population is £47,911 per QALY gained. The ICERs for pembrolizumab combination therapy versus standard care were estimated to be £62,619 and £37,669 per QALY gained for the PD-L1 TPS <1% and TPS 1-49% subgroups, respectively. Within the TPS ≥50% subgroup, the ICER for pembrolizumab combination therapy versus pembrolizumab combination therapy was estimated to be £16,097 saved per QALY lost (South-West quadrant). Given concerns regarding the robustness of the indirect comparison, the results for the PD-L1 TPS ≥50% may not be reliable.

The company's base case model suggests that mean survival in the standard care group is 2.26 years; the model suggests that a small proportion of patients will be long-term survivors (probability of survival at 10-years = 0.04). The ERG is uncertain whether NICE's EoL criteria are met.

7. REFERENCES

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Appendix 1: Technical appendix – instructions for implementing the ERG's exploratory analyses within the company's model

ERG exploratory analysis 1: TTD (pembrolizumab combination therapy group only).

In the company's model, go to worksheet 'Model Settings', and change the selection of the 'Source of ToT inputs' for pembrolizumab combination therapy in the dropdown menu in cells I37:L37 to 'Time-on-treatment data from KN407'.

ERG exploratory analysis 2: Distribution of subsequent-line treatment (pembrolizumab combination therapy and standard care groups)

In the company's model, go to worksheet 'Regimen Costs UK', and replace the values in cells C125:D134 with the values in Table A1.

Table A1: ERG's updated distribution of subsequent-line therapies

Subsequent-line treatment	Pembrolizumab combination therapy	Standard care
Atezolizumab	0.0%	[redacted]
Pembrolizumab	0.0%	[redacted]
Carboplatin plus gemcitabine	[redacted]	[redacted]
Carboplatin plus paclitaxel	[redacted]	[redacted]
Cisplatin plus gemcitabine	[redacted]	[redacted]
Cisplatin plus paclitaxel	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]

ERG exploratory analysis 3: Application of treatment effect waning for PFS

In the company's model, go to worksheet 'Modeled PFS, and apply the following changes:

- change the formula in cell M9 to '=IF(AND(pembro.waning="yes",C9/(365.25/7)>= pembro.waning.yr),M8*(N9/N8),'Pembro Chemo PFS'!$F9)'. Drag the formula down to row 2,096;
- change the formula in cell U9 to '=IF(AND(pembro.waning="yes",C9/(365.25/7)>= pembro.waning.yr),U8*(V9/V8),'Pembro Chemo-PD1 >=50% PFS'!$F9). Drag the formula down to row 2,096;
- change the formula in cell W9 to '=IF('Model Settings'!M50=2,'NMA-ITC PFS (tvarHR)'!BT9,IF(AND(pembro.waning="yes",C9/(365.25/7)>=pembro.waning.yr),W8*(V9/V8), 'NMA-ITC PFS (conHR)'!AS9)). Drag the formula down to row 2,096;

- change the formula in cell AC9 to '=IF(AND(pembro.waning="yes",C9/(365.25/7)>= pembro.waning.yr),AC8*(AD9/AD8),'Pembro Chemo-PD1 1-49% PFS'!$F9). Drag the formula down to row 2,096;
- change the formula in cell AK9 to '=IF(AND(pembro.waning="yes",C9/(365.25/7)>= pembro.waning.yr),AK8*(AL9/AL8),'Pembro Chemo-PD1 <1% PFS'!$F9). Drag the formula down to row 2,096.

ERG exploratory analysis 4: ERG preferred base case

The ERG's preferred base case analysis includes ERG exploratory analyses 1, 2 and 3; therefore, apply all the changes listed above.

All sensitivity analyses undertaken by the ERG were applied separately to the ERG's preferred base case version of the model.

ERG sensitivity analysis 1: Choice of OS model

In the company's model, go to worksheet 'Model Settings' and change the curve selections in both dropdown menus in cells I68:K68 and I70:K70, selecting, respectively, the options 'Exponential', 'Weibull', 'Log-normal' 'Log-logistic (base-case)' 'Gompertz' and 'Generalised Gamma'.

ERG sensitivity analysis 2: Choice of PFS model

In the company's model, go to worksheet 'Model Settings' and change the curve selections in both dropdown menus in cells I59:J59 and I61:J61, selecting, respectively, the options 'Exponential', 'Weibull', 'Log-normal (base-case)' 'Log-logistic' 'Gompertz' and 'Generalised Gamma'.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1683]

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

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

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 20 November 2020** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

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

Issue 1 ERG final Report

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 8 states "it is anticipated that the company will provide an amended indirect comparison analysis during the technical engagement stage."	"The company provided an amended indirect comparison analysis at a later time point."	MSD provided the additional analyses request by the ERG on 6th April 2020 as agreed.	This is not a factual inaccuracy. As described in the ERG report, the requested analyses were not provided before the ERG report was submitted (30th March). The company's additional analyses provided in April are described and critiqued in a separate ERG addendum. No amendment is required.

Issue 2 ERG Final Report

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15 states "At the time of entry into the CDF, the managed entry agreement included a Patient Access Scheme (PAS) which took the form of a simple price discount of [redacted]%. At the time of writing, this PAS remains in place. "	It was communicated to NICE on 14th August 2020 that there is an updated PAS in place for KEYTRUDA. MSD will resend this e-mail to Gavin Kenny once this document has been submitted via NICE docs.	MSD would like to inform the ERG and NICE of this update due to the relevance of the cost effectiveness analyses.	This is not a factual inaccuracy. This PAS was updated after the ERG report was submitted (30th March). Additional analyses have been presented by the ERG using the updated November 2020 PAS - these are provided in a separate appendix to the ERG report.

Issue 3 ERG Final Report

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 21 states “[redacted]”	This statement should be omitted.	In TA600 it was confirmed by clinical experts that pembrolizumab combination therapy should be given first-line in some patients who are high expressors as per the FAD. This includes people who need an urgent, rapid response may benefit from initial combination therapy with pembrolizumab and chemotherapy (for example, those with bulky central disease). The committee agreed that an additional treatment option would benefit people with untreated, squamous NSCLC and concluded that pembrolizumab combination therapy would be a welcome additional treatment option.	This is not a factual inaccuracy. The ERG believes that there is uncertainty around the choice of first-line treatments for this patient group, hence the need for this CDF review. The excerpt of the ERG report quoted in the company’s factual accuracy check relates to uncertainty around the comparison between pembrolizumab combination and pembrolizumab monotherapy in patients with PD-L1 TPS ≥50%, where the HRs for OS for pembrolizumab combination versus control in KEYNOTE-407 are less favourable than those for pembrolizumab monotherapy versus control in KEYNOTE-042 after 6 months and through to 24 months. The text provided in the ERG report is factually accurate. The NICE TA600 guidance states that “*Because the*

			clinical evidence is immature, the cost-effectiveness estimates for pembrolizumab combination therapy are very uncertain. It may meet NICE's criteria to be considered a life extending treatment at the end of life when compared with standard chemotherapy, ***but there is uncertainty about this. It does not meet the end-of-life criteria when compared with pembrolizumab monotherapy for people whose tumours express PD-L1 with a tumour proportion score of 50% or higher.***" (Page 4). The guidance also states that there is unmet clinical need for treatment options in this area, and that during the committee meeting, clinical experts stated that "*…while* ***most clinicians would use pembrolizumab monotherapy for people whose tumours express PD-L1 at 50% or higher to avoid the additional toxicity of chemotherapy, a few people who need an urgent, rapid response may benefit from initial combination therapy***

			with pembrolizumab and chemotherapy (for example, those with bulky central disease). *… The committee agreed that an additional treatment option would benefit people with untreated, squamous NSCLC and concluded that pembrolizumab combination therapy would be a welcome additional treatment option."* The report has not been amended.

Issue 4 ERG Final Report

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 45 states "In response to a request for clarification from the ERG (see clarification response,[10] question B1), the company stated that a small number of patients with PD-L1 TPS ≥50% ([redacted]) in the intervention arm of KEYNOTE-407 received a second course of pembrolizumab; no patients in the control arm of KEYNOTE-042 received a second course of pembrolizumab.	"the company stated that a small number of patients with PD-L1 TPS ≥50% ([redacted]) in the intervention arm of ***KEYNOTE-042*** received a second course of pembrolizumab; [redacted] patients in the ***pembrolizumab*** arm of ***KEYNOTE-407*** received a second course of pembrolizumab."	The number of patients receiving second course of treatment as quoted in the ERG report are referring to the opposite KEYNOTE trials. In addition, the ERG report states, "no patients in the control arm" whilst the clarification question B1 asked for the number of patients in the pembrolizumab arm.	The ERG agrees that this was a factual inaccuracy; the report has been amended.

Issue 5 ERG Final Report

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 46, "Although the CDF-CS mentions an imbalance in the use of immunotherapies between KEYNOTE-042 and KEYNOTE-047, it does not discuss potential treatment effect modifiers and their potential impact on the indirect comparison."	"Although the CDF-CS mentions an imbalance in the use of immunotherapies between KEYNOTE-042 and KEYNOTE-047, the company provided an additional analysis in response to the clarification questions which incorporate potential treatment effect modifiers"	This additional analyses was provided at a later date as agreed with NICE and the ERG.	This is not a factual inaccuracy. As described in the ERG report, the requested analyses were not provided before the ERG report was submitted (30th March). The company's additional analyses provided in April are described and critiqued in a separate ERG addendum. No amendment is required.

Issue 6 ERG Final Report

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 46: "The company's indirect comparison assumes that PFS follows a log-logistic distribution. However, the company's economic model assumes that PFS follows the empirical Kaplan-Meier function followed by a log-normal distribution. This approach is inconsistent."	Suggestion to remove the statement as it implies that the selection of different parametric curves between the trial comparison and the ITC comparison makes the analyses non-robust	Other distributions were evaluated for modelling the time-varying HRs for PFS and the log-logistic was found to be the best fitting. There is no reason to expect that the PFS curve for a trial comparator and the HR for an indirect comparison of PFS between an indirect comparator and a trial comparator, would follow the same statistical distribution. They are different	This is not a factual inaccuracy. The ERG considers that the approach taken by the company is inconsistent. The ERG also reiterates that HRs are irrelevant in the case of the log-logistic and log-normal models. However, the ERG considers it unlikely that this issue would meaningfully affect the conclusions of the analysis

		estimations and involve different comparators, so it seems most appropriate to select the best fitting option for each comparison, whether the same or different distributions.	for the TPS≥50% subgroup.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG Response
ERG Final Report, page 36, table 12	This table should be marked [redacted]	As requested by MSD in October the outputs of the timevarying ITC should be marked CIC. The documents were resubmitted via NICE docs by MSD on 19th October 2020.	The CIC marking has been amended.
ERG addendum, page 4, table 1	This table should be marked [redacted]	As requested by MSD in October the outputs of the timevarying ITC should be marked CIC. The documents were resubmitted via NICE docs by MSD on 19th October 2020.	The CIC marking has been amended.

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]

Evidence Review Group Report Addendum: ERG commentary on additional analyses submitted by the company

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	1st May 2020 (includes factual accuracy check amendments)

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number NIHR130472.

1. Introduction

This addendum provides a brief summary and critique of the company's responses to the ERG's clarification questions[1] B4, B6, and B8, which were provided following the submission of the ERG report.[2] All three of these questions relate to the company's indirect comparison of pembrolizumab combination therapy versus pembrolizumab monotherapy in patients with a PD-L1 TPS ≥50% based on KEYNOTE-407 and KEYNOTE-042. The company's responses to the other clarification questions, and the ERG's view regarding these responses, remain unchanged; further details are provided in the ERG report.[2]

2. Summary and critique of the company's additional clarification responses provided following the submission of the ERG report

2.1. Summary of company's additional analyses

The company's additional clarification response document includes four additional sets of analyses:

Additional analysis 1: Re-analysis of the indirect comparison including re-censoring for the control arms of KEYNOTE-407 and KEYNOTE-042 (response to ERG clarification question B4). This analysis estimates time-varying hazard ratios (HRs) for pembrolizumab monotherapy versus pembrolizumab combination therapy, including treatment switching adjustment using the 2-stage method, assuming that survival in each treatment group follows a log-logistic distribution, based on an ITC performed using Bucher method.[3] The company's additional clarification response[1] presents: the parameters of the log-logistic OS distribution for each trial arm (including switching adjustment); time-varying HRs at months 1, 3, 6, 9, 12, 15, 18, 21 and 24, and Kaplan-Meier plots for each trial including adjustment for treatment switching including re-censoring.

Additional analysis 2: Re-analysis of the indirect comparison using the failure odds transformation of the log-logistic distribution (response to ERG clarification question B6). This analysis estimates time-varying odds ratios (ORs) for pembrolizumab monotherapy versus pembrolizumab combination therapy, including treatment switching adjustment using the 2-stage method, assuming that survival in each treatment group follows a log-logistic distribution, based on an ITC performed using Bucher method.[3] Re-censoring is not applied in this analysis. The company's additional clarification response[1] presents the parameters of the log-logistic OS distribution for each trial arm (including switching adjustment) and time-varying ORs at months 1, 3, 6, 9, 12, 15, 18, 21 and 24. Kaplan-Meier plots for each trial with adjustment are not reported for this analysis.

Additional analysis 3: Re-analysis of the indirect comparison including population-adjustment without treatment switching adjustment (response to ERG clarification question B8). This analysis estimates time-dependent HRs for pembrolizumab monotherapy versus pembrolizumab combination therapy,

assuming that survival in each treatment group follows a log-logistic distribution, based on an ITC performed using Bucher method.[3]. Treatment switching adjustment and re-censoring are not applied in this analysis. The analysis includes five potential treatment effect modifiers, which were included based on clinical input: European Cooperative Oncology Group (ECOG) performance status (PS) (0 vs. 1 or 2), smoking status, age, gender and tumour size. Inverse probability of treatment weighting (IPTW) was used to balance the treatment groups within each trial and across both trials. The company's additional clarification response[1] presents: the inverse probability weights; patient characteristics in each trial before and after applying weighting; parameters of the log-logistic OS distribution for each trial arm (excluding switching adjustment); time-varying HRs at months 1, 3, 6, 9, 12, 15, 18, 21 and 24, and Kaplan-Meier plots for each trial.

Additional analysis 4: Re-analysis of the indirect comparison including both population-adjustment and treatment switching adjustment (question B8). This analysis is the same as additional analysis 3, but treatment switching adjustment is included. Re-censoring is not included. The company's clarification response[1] presents the parameters of the log-logistic OS distribution for each trial arm (excluding switching adjustment), time-varying HRs at months 1, 3, 6, 9, 12, 15, 18, 21 and 24, and Kaplan-Meier plots for each trial with switching adjustment.

The time-varying treatment effects for OS for pembrolizumab monotherapy versus pembrolizumab combination therapy from the company's original CDF-CS[4] and each of the company's four additional analyses[1] are summarised in Table 1. As shown in the table, all analyses indicate that by 12 months (or earlier), the treatment effect favours pembrolizumab monotherapy compared with pembrolizumab combination therapy, irrespective of adjustments for imbalances between trial arms, adjustment for treatment switching and re-censoring. These estimates are however uncertain, and the 95% confidence intervals for many of the time-dependent treatment effects cross 1.0.

Table 1: Time varying hazard ratios for OS from ITC of pembrolizumab monotherapy vs. pembrolizumab combination therapy (log-logistic distribution), PD-L1 TPS ≥ 50% population

Time point (months)	Treatment effect for OS (95% CI) – pembrolizumab monotherapy versus pembrolizumab combination therapy				
	Company's original CDF-CS analysis:* - Time-varying HR - Adjusted for switching - No re-censoring - No population-adjustment	**Company's additional analysis 1:†** - Time-varying HRs - Adjusted for switching - With re-censoring - No population-adjustment	**Company's additional analysis 2:†** - Time-varying ORs - Adjusted for switching - No re-censoring - No population-adjustment	**Company's additional analysis 3:†** - Time-varying HRs - Not adjusted for switching - No re-censoring - With population-adjustment	**Company's additional analysis 4:†** - Time-varying HRs - Adjusted for switching - No re-censoring - With population-adjustment
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HR: hazard ratio; OR: odds ratio
** Original analysis reported in the CDF-CS[4]*
† New analyses reported in the company's additional clarification response[1]

2.2. ERG's critique of company's additional analyses

With respect to the company's further analyses, the ERG notes the following:

- The company has provided the analyses requested by the ERG.
- With respect to additional analysis 2, the company's clarification response[1] notes that whilst the incorporation of re-censoring in the treatment switching adjustment may avoid informative censoring, this can introduce additional bias through the potentially important loss of information. As such, the company comments that this analysis should be viewed with caution. The ERG agrees with this view but notes that, despite this potential bias, it is important to assess whether re-censoring has an impact on the results of the analysis. As shown in Table 1, re-censoring does have some impact on the estimated treatment effects, but the general trend remains consistent with the analysis which excludes re-censoring.
- It is unclear why the company has not included re-censoring in additional analyses 3 and 4 – this may be due to the company's concerns regarding potential bias, although this is not explicitly stated in the company's clarification response.
- The company's original ITC and all four additional analyses indicate the same general trend, whereby the estimated treatment effect favours the pembrolizumab monotherapy within 12 months or earlier.
- Despite presenting a number of complex indirect comparisons, the company has not included the results of these additional analyses within their health economic model.
- As noted in the appendices to the CDF-CS, the reason underlying the more favourable results for pembrolizumab monotherapy are unclear. The company speculates that adding chemotherapy may adversely impact on outcomes for patients who discontinue treatment or otherwise experience poorer health outcomes due to the side effects of chemotherapy.

3. Additional exploratory analyses undertaken by the ERG

The ERG undertook additional analyses to explore the impact of applying these new time-varying treatment effect estimates within the company's health economic model. For additional analysis 1 (re-censoring) and additional analysis 4 (population-adjustment and switching adjustment), the ERG inputted the reported HRs directly into the economic model, thereby retaining all of the company's other assumptions about interpolation of treatment effects between reported timepoints and loss of the treatment effect over time. For additional analysis 2 (failure odds transformation), the ERG was unable to apply the company's assumptions about treatment waning or interpolation of treatment effects between timepoints; instead, the ERG's analysis for this model uses the exact estimates of the adjusted OR at each weekly timepoint up to 24 months, and subsequently assumes that the treatment effect between the groups is lost; this simplifying assumption favours the pembrolizumab combination therapy group compared with the company's other analyses based on time-varying HRs. Results for additional

analysis 3 were not included in the economic analysis, as these reflect the ITT analyses of the trials without adjustment for treatment switching; hence, these are likely to be biased. It should be noted that the ERG's additional exploratory analyses are subject to two issues: (i) it is inappropriate to apply HRs to the log-logistic distribution, and; (ii) the company's additional indirect comparisons have been applied only to OS, hence the company's original time-varying HRs for PFS are applied in all additional analyses undertaken by the ERG. The ERG does not expect these issues to affect the general conclusions of the economic analyses.

The results of the ERG's additional exploratory analyses are presented in Table 2. All three analyses suggest that pembrolizumab monotherapy generates more LYGs, QALYs and costs than pembrolizumab combination therapy, hence the ICERs from the company's original analysis and the ERG's additional exploratory analyses lie in the South-West quadrant of the cost-effectiveness plane. These ICERs are estimated to range from £13,439 to £27,124 saved per QALY lost.

Table 2: ERG preferred analysis deterministic results, pembrolizumab combination therapy versus pembrolizumab monotherapy, PD-L1 TPS ≥50% subgroup

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG original preferred CDF-CS analysis[2]							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£16,097 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's additional analysis 1 (with re-censoring)							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£13,439 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's additional analysis 2 (failure odds transformation)†							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£14,336 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's additional analysis 4 (with population-adjustment and switching adjustment)							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£27,124 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; TTD - time to treatment discontinuation; PFS - progression-free survival; SWQ - South-West quadrant
**undiscounted*
† Treatment effect (OR) applied for 2 years based on company's indirect comparison; subsequently the OR is assumed to be 1.0. The company's other ITC analyses interpolate HRs between timepoints, assume that the 24-month HR is maintained until month 36, and that by year 5, the HR increases to 1.0

4. References

1. Merck, Sharpe and Dohme. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]. Company's response to additional clarification questions from the ERG (April 2020). MSD: Hertfordshire, UK; 2020.
2. Tappenden P, Navega Biz A, Uttley L, Stevens JW. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]. Evidence Review Group report. University of Sheffield: Sheffield, UK; 2020.
3. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology* 1997;50:683-91.
4. Merck, Sharpe and Dohme. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]. Company's evidence submission to the National Institute for Health and Care Excellence. MSD: Hertfordshire, UK; 2020.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1683]

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

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

Deadline for comments **12 July 2021**

Thank you for your time.

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

Notes on completing this form

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

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

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

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

About you

Your name	Carl Selya-Hammer
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	MSD
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

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Key issues for engagement

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

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td>Key issue 1: Uncertainty surrounding the long-term treatment effect of pembrolizumab combination therapy on progression free survival and overall survival</td><td>YES</td><td>Subsequent to the company submission in March 2020, for which the cost-effectiveness model was updated with data from the Final Analysis of KEYNOTE-407 based on a May 2019 data cut, follow-up survival data were collected and reported in a poster at the European Lung Cancer Congress (ELCC) in March 2021.[i] Based on this 30-Sept-2020 data cut, survival outcomes at a minimum of 3 years follow-up show a maintenance of treatment benefit from the Final Analysis, both in terms of progression-free survival (PFS) and overall survival (OS), as seen below within the top-line results presented in the poster.

In particular, the OS hazard ratio (HR) for pembrolizumab + chemo remained at 0.71 at 3-years' follow-up with a slightly narrower confidence intervals in this follow up data cut:

• Final analysis OS HR: 0.71 (0.58-0.88), median follow-up 14.3 months
• 3-year follow-up OS HR: 0.71 (0.59-0.86)
• Median OS gain with the pembrolizumab + chemo combination vs SoC (ITT population): 5.6 months

<table>
<tr><th></th><th>Pembro + Chemo (n = 278)</th><th>Placebo + Chemo (n = 281)</th></tr>
<tr><td>Median OS, mo (95% CI)</td><td>17.2 (14.4–19.7)</td><td>11.6 (10.1–13.7)</td></tr>
</table>
</td></tr>
</table>

OS HR (95% CI)	0.71 (0.59–0.86)	-
3-y OS rate, % (95% CI)	29.7 (24.5–35.2)	18.2 (13.8–23.0)
Median PFS, mo (95% CI)	8.0 (6.3–8.5)	5.1 (4.3–6.0)
PFS HR (95% CI)	0.59 (0.49–0.71)	-
3-y PFS rate, % (95% CI)	16.1 (12.0–20.8)	6.5 (3.9–10.0)
Median PFS2,[a] mo (95% CI)	13.8 (12.2–15.9)	9.1 (8.0–10.3)
PFS2 HR (95% CI)	0.59 (0.49–0.71)	-
ORR, % (95% CI)	62.6 (56.6–68.3)	38.8 (33.1–44.8)
Median DOR, mo (range)	9.0 (1.3+ to 45.0+)	4.9 (1.3+ to 44.8+)
+, indicates no PD at last disease assessment. [a]Time from randomization to second/subsequent PD on next-line treatment/death		

In sum, the additional follow-up data strongly reinforce the treatment benefits associated with pembrolizumab + chemo combo in terms of PFS and OS results which were reported in the final analysis.

The updated survival data in the 30-SEPT-2020 data cut (PFS and OS Kaplan-Meier [KM] plots) were parametrized using the same methods as were performed in the March 2020 company submission. For OS for both treatment arms, the one-piece log-logistic model fit the data best using the updated KM data (lowest AIC/BIC), consistent with the original company submission including the May 2019 data cut. The results were also consistent with 3-year, 5-year survival rates observed in the literature for this patient population. While we have not had the opportunity to test these values with clinical experts, they are consistent with the previous submission for which landmark survival estimates were validated by clinical experts and whose feedback informed the choice of survival extrapolation for PFS and OS. The updated extrapolated curves were not able to be integrated into the cost-effectiveness model before the end of technical engagement, however, the updated curves and the cumulative survival probabilities for 6 survival models for PFS and OS for each treatment arm are included in MSD's response to technical engagement as a separate Excel® file. Given the

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		consistency with the survival outcomes between the final analysis and the 3-year follow-up data, there is increasing certainty that pembrolizumab provides a long-term OS and PFS benefit over standard chemotherapies in the first-line treatment of squamous NSCLC.
Key issue 2: No additional safety data are presented in the company submission for the CDF review	NO	MSD wishes to highlight three points regarding this key issue. Firstly, no new safety issues were identified in the final analysis. Secondly, adverse event incidence has not been previously identified as a key driver of the cost effectiveness estimates and it is unlikely that long-term adverse event data will have an impact on the most current cost effectiveness estimates. Lastly, drug safety is of paramount importance to MSD and is monitored on an ongoing basis.
Key issue 3: Committee's preferred assumptions regarding subsequent immunotherapy use do not reflect experience of KEYNOTE-407	NO	As the ERG has noted, the mix of subsequent therapies given to patients initially treated with standard chemotherapies was not identified as a source of uncertainty to be resolved through additional data collection during the Cancer Drugs Fund period. For this reason, this issue was not included in the Terms of Engagement for this appraisal. The committee's assumption on subsequent therapies upon CDF entry was that all patients initially treated with standard chemotherapies who received a subsequent therapy would receive an immunotherapy (i.e. atezolizumab or pembrolizumab monotherapy). To gain clarity on this issue, MSD engaged with 10 clinicians in one-on-one interviews. Clinician profiles were as follows: • 9 medical oncologists, 1 respiratory physician • 9 based in English centres (SW, SE, London, Midlands, NE), 1 in Wales • All >5 years consultant clinical experience Regarding the issue of subsequent therapy in UK clinical practice, clinicians were asked: "If a patient with metastatic NSCLC, squamous histology, and any TPS (0-100%) had received first line chemotherapy, what category of treatment would you give second line (assuming the patient was eligible for any NICE approved therapy)?"

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		All clinicians replied that these patients would receive single agent immunotherapy 100% of the time. Considering the unanimity of clinician feedback on this issue, it's clear that the assumptions around subsequent therapy for chemotherapy-treated patients included in the company base case reflects current clinical practice. During the technical engagement discussion between NICE, the ERG and MSD, it was noted that KEYNOTE-407 does not fully reflect UK practice, as such there is some uncertainty regarding the efficacy outcomes observed in the trial compared to those that would be observed in real world practice. In discussion, no obvious methodology to adjust trial outcomes data to better reflect expected real world benefit could be identified. All potential methods of adjustment require additional assumptions and are associated with uncertainty. MSD would assert that while imperfect, the company base case is sufficient for decision making on this point.
Key issue 4: The indirect comparison for the PD-L1 tumour proportion score ≥50% subgroup presented in the company submission for the CDF review is not robust	NO	This issue was discussed at the technical engagement meeting between NICE, the ERG and MSD. It was agreed at this meeting that the additional analyses MSD provided in response to ERG clarification questions regarding the indirect comparison provided sufficient clarity on this issue.
Key issue 5: Uncertainty concerning whether pembrolizumab combination therapy meets NICE's End-of-Life criteria	NO	Regarding End of Life, the first criterion is, "The treatment is indicated for patients with a short life expectancy, normally less than 24 months". The most recent data cut, see table above, report a median OS of less than 12 months for the SoC arm: median OS was 11.6 months. Therefore, based on the clinical trial data this indication clearly meets the first criterion. The cost-effectiveness model submitted by the company predicts a mean OS for the SoC arm in the ITT population of 27.1 months. However, the ERG notes that only 28% of patients treated with standard chemotherapy in KEYNOTE-407 were alive at 24 months' follow-up. In other

		words, the vast majority (greater than two-thirds) of untreated people with squamous NSCLC in the KEYNOTE-407 trial do not survive beyond 24 months. As to whether the 3-month OS gain criterion is met, the ERG notes that there is uncertainty as to the long-term OS benefit associated with pembrolizumab combination therapy. The maintenance of the OS benefit (0.71 HR) from the final analysis to the 30-Sept-2020 data cut submitted as part of the additional evidence to technical engagement provides sufficient certainty that this 3-month OS gain can be expected to be maintained in the long term. The OS gain reported in the table above indicates a median OS gain of 5.6 months for pembrolizumab combination compared with SoC. MSD note that due to the availability of pembrolizumab monotherapy in the >50% PD-L1 population, the ERG has looked into whether EoL criteria are met in the subgroups of the population included within KEYNOTE-407. However, we note that subgrouping in this way is not in line with the trial protocol, which did not stratify for PD-L1 greater and less than 50%. We also note that clinicians would not use the pembrolizumab + chemo combo if they thought pembrolizumab monotherapy would produce sufficient effect, which is in line with the CDF restriction for the pembrolizumab + chemo combo, as reported below: • *"Either the patient has a PD-L1 TPS of 0-49% or has a PD-L1 TPS of 50-100% and requires an urgent clinical response (e.g. major impending airway obstruction) so as to justify the use of the combination of pembrolizumab carboplatin and paclitaxel rather than pembrolizumab monotherapy and this issue has been fully discussed with the patient*." This proposed restriction (i.e. patients not suitable for pembrolizumab monotherapy) is in line with current usage in the CDF which requires urgent clinical need. Clinicians are consistent in expressing they would only use pembrolizumab + chemo in patients that have an urgent clinical need. Reasons they list include • Critical airway (trachea/main bronchus) at risk of occlusion from bulky disease

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		• Major vessels (e.g. superior vena cava) at risk of occlusion • Rapid clinical progression • Rapid progression on sequential imaging • Large number of organs involved • Large or numerous liver metastases • High symptomatic burden e.g. patient suffering from significant pain, anorexia, paraneoplastic syndromes. Therefore, MSD suggests that the decision should be based on the ITT population, in which EoL criteria has been shown to be met. Though we understand a statement that for the >50% patients pembrolizumab monotherapy should be first choice and pembrolizumab + chemo combo should be reserved for patients who require a rapid response, according to clinician expertise. Lastly, recent technical appraisals in NSCLC (e.g. ID1566, Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer) have seen agreement from clinical experts, the ERG and the NICE technical team that for the squamous subgroup with PD-L1% < 50%, survival with current therapies is less than 24 months.

References

[i] 97O - First-Line Pembrolizumab Plus Chemotherapy for Patients With Advanced Squamous NSCLC: 3-Year Follow-up From KEYNOTE-407. Journal of Thoracic Oncology (2021) 16 (suppl_4): S748-S802. https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-virtual-congress-2021/first-line-pembrolizumab-plus-chemotherapy-for-patients-with-advanced-squamous-nsclc-3-year-follow-up-from-keynote-407

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Clinical expert statement & technical engagement response form

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1683]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please return this form by **5pm** on **Monday 12 July 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with untreated metastatic squamous non-small-cell lung cancer and current treatment options	
About you	
1. Your name	**Yvonne Summers**
2. Name of organisation	**The Christie Hospital NHS Foundation Trust, Manchester**
3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with untreated metastatic squamous non-small-cell lung cancer ? **X**☐ a specialist in the clinical evidence base for untreated metastatic squamous non-small-cell lung cancer or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X**☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
The aim of treatment for untreated metastatic squamous non-small-cell lung cancer	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity	

by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in untreated metastatic squamous non-small-cell lung cancer ?	
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase	

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or	

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

• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in	

the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA600]?	
23. How do data on real-world experience compare with the trial	

data?	
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	
24b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

Key issue 1: Uncertainty surrounding the long-term treatment effect of pembrolizumab combination therapy on progression free survival and overall survival	Data have been presented on longer follow up in Keynote 407 (median 14.3 months) with sustained improvement in OS (17.1 months vs 11.6 months for combination treatment and chemotherapy respectively) and PFS (8.0 months vs 5.1 months). However it would be helpful to see more mature follow up to give further assurance about the size of the longterm benefit of treatment. Other studies have confirmed the longterm benefit of immunotherapy with longer follow up than the 14.3 months described in KEYNOTE 407. The potential advantage for patients receiving combination chemotherapy-immunotherapy up front is that all patients access treatment, whereas when a sequential approach is taken, less than 50% of patients will access subsequent therapy.
Key issue 2: No additional safety data are presented in the company submission for the CDF review	Longer follow up from a number of immunotherapy studies including KEYNOTE 407 has not raised and safety concerns either from new adverse events or increased frequency. Patients can experience adverse events at almost anytime during treatment and for at least 6 weeks after completing therapy.
Key issue 3: Committee's preferred assumptions regarding subsequent immunotherapy use do not reflect experience of KEYNOTE-407	The ERG note that in KEYNOTE 407 about 15% of subsequent therapy in the control arm was chemotherapy, whereas the company modelling suggested that immunotherapy would be the next line of treatment. When KEYNOTE 407 was recruiting not all centres would have had access to immunotherapy as a subsequent treatment and so, at that time more chemotherapy, may have been the only option to the patients. None of these patients would have other reasons to be excluded from immunotherapy treatment as they had been deemed eligible for entry to the trial. In the current treatment environment these patients would have access to second line immunotherapy and further chemotherapy would be highly unlikely to be the next treatment of choice (1% or less)
Key issue 4: The indirect comparison for the PD-L1 tumour proportion score ≥50% subgroup presented in the	Health economists to comment

company submission for the CDF review is not robust	
Key issue 5: Uncertainty concerning whether pembrolizumab combination therapy meets NICE's End-of-Life criteria	For patients with Squamous NSCLC treated with chemotherapy and immunotherapy combinations the median overall survival is consistently less than 24 months (checkmate 9LA - 14.5 months for squamous cohort; IMPOWER 131 - 14.2 months)
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Combination with carboplatin paclitaxel and pembrolizumab has become the SoC for selected (PS0-1) patients with Stage 4 Squamous NSCLC
- Combination with carboplatin paclitaxel and pembrolizumab offers improved OS, PFS, ORR and DoR compared to chemotherapy alone
- Combination with carboplatin paclitaxel and pembrolizumab offers improved prospects for long term control of disease compared to chemotherapy alone, however a proportion of patients are not for enough for the combination treatment due to poor PS and/or significant co-morbidity
-

•

Thank you for your time.

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

.....

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The information that you provide on this form will be used to contact you about the topic above.

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Technical engagement response form

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1683]

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

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

Deadline for comments **12 July 2021**

Thank you for your time.

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

Notes on completing this form

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

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

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

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

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Royal College of Pathologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosures to declare**

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Key issues for engagement

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

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty surrounding the long-term treatment effect of pembrolizumab combination therapy on progression free survival and overall survival	**YES/NO**	I do not have particular expertise relevant to this issue.
Key issue 2: No additional safety data are presented in the company submission for the CDF review	**YES/NO**	I do not have particular expertise relevant to this issue.
Key issue 3: Committee's preferred assumptions regarding subsequent immunotherapy use do not reflect experience of KEYNOTE-407	**YES/NO**	I do not have particular expertise in evaluating the data presented.
Key issue 4: The indirect comparison for the PD-L1 tumour proportion score ≥50% subgroup presented in the company	**YES/NO**	I do not have particular expertise relevant to this issue.

submission for the CDF review is not robust		
Key issue 5: Uncertainty concerning whether pembrolizumab combination therapy meets NICE's End-of-Life criteria	**YES/NO**	I do not have particular expertise relevant to this issue.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer: CDF guidance review [ID1683]

Addendum: ERG response to company's technical engagement response and updated analyses including the confidential PAS discount for pembrolizumab

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	23rd July 2021

1. Introduction

This document provides a brief commentary on the company's technical engagement response.[1] This should be read in conjunction with the ERG report[2] and the subsequent ERG addendum.[3] All results presented in this document include the Patient Access Scheme (PAS) discount for pembrolizumab, but exclude confidential comparator PAS discounts. With exception of the company's base case analysis presented in the original ERG report, these results also include updated prices for other drugs (paclitaxel, docetaxel, carboplatin, cisplatin, gemcitabine, and vinorelbine – see Appendix 1).

2. ERG critique of the company's response to key issues for technical engagement

Key issue 1*: Uncertainty surrounding the long-term treatment effect of pembrolizumab combination therapy on progression free survival and overall survival*

The company's technical engagement (TE) response[1] highlights that the company's submission (the CDF-CS[4]) included data from the May 2019 data-cut of KEYNOTE-407[5] and that longer-term data have since become available. These longer-term data were presented as a poster at the European Lung Cancer Congress (ELCC) in March 2021.[6] The company notes that the point estimate of the hazard ratio (HR) for overall survival (OS) from the later 2020 data-cut of KEYNOTE-407 is the same as that for the May 2019 data-cut, but the 95% confidence interval (CI) is slightly narrower (2020 data-cut HR=0.71, 95% CI 0.59 to 0.86; 2019 data-cut HR=0.71, 95% CI 0.58 to 0.88). The company's TE response also reports further data on OS, progression-free survival (PFS), overall response rate (ORR) and duration of response (DoR) from the later data-cut; for brevity, these are not reproduced here. The company states that the additional follow-up data strongly reinforce the treatment benefits observed in the final analysis. The ERG agrees that these additional data reduce uncertainty regarding long-term treatment effects for pembrolizumab combination therapy.

As part of their TE response,[1] the company provided updated Kaplan-Meier (KM) plots for time to treatment discontinuation (TTD), PFS and OS and updated parametric survival models for OS for the intention-to-treat (ITT) population. The company did not incorporate these into their economic model. As part of this addendum, the ERG has included the updated OS models in the economic model. However, the ERG was unable to update PFS as this was based on hybrid models (KM functions up to 26 weeks followed by log-logistic models) and the company provided the KM estimates but not the re-fitted log-logistic model parameters for this endpoint. For the same reason, the ERG has also not updated the TTD models.

Table 1 presents the results of the company's updated base case analysis for the ITT population using the previous PAS discount for pembrolizumab and models fitted to the 2019 data-cut,[2] and shows the individual impacts of including the updated PAS discount and other drug prices and the updated OS

models based on the 2020 data-cut of KEYNOTE-407. Table 2 presents the results of the ERG's preferred analysis (originally presented in Table 16 of the ERG report[2]) using the updated OS models based on the 2020 data-cut and the latest PAS discount and drug prices.

After accounting for the updated PAS for pembrolizumab and drug prices, the inclusion of the updated parametric survival models for OS has a fairly minor impact on the company's base case results (company's base case: 2020 data-cut incremental cost-effectiveness ratio [ICER] = £25,431 per quality-adjusted life year [QALY] gained; 2019 data-cut ICER = £27,718 per QALY gained). Similarly, the inclusion of the longer-term OS data in the ERG's preferred analysis has a fairly minor impact on the ICER (ERG's preferred analysis: 2020 data-cut ICER = £33,961 per QALY gained; 2019 data-cut ICER = £36,973 per QALY gained).

The ERG notes that these analyses are subject to some limitations. As discussed above, the company has not provided re-fitted PFS and TTD model parameters using the 2020 data-cut of KEYNOTE-407; hence, these models are instead based on the 2019 data-cut. The ERG also notes that the company has not provided updated models for the programmed death-ligand 1 (PD-L1) subgroups and so the ERG has been unable to update the economic subgroup analyses.

Table 1: Company's updated cost-effectiveness results, ITT population, deterministic, using May 2019 and September 2020 data-cuts and original and latest PAS discounts

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case, using final analysis (data cut-off May 2019) – original PAS (ERG report, March 2020, discount=)							
Pembrolizumab combination							**£38,090**
Standard care				-	-	-	-
Company's updated base case, using final analysis (data cut-off May 2019) – updated PAS (discount=) and prices							
Pembrolizumab combination							**£27,718**
Standard care				-	-	-	-
Company's updated base case, using longer-term OS models (data cut-off September 2020, discount=)							
Pembrolizumab combination							**£25,431**
Standard care				-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ITT - intention-to-treat.
** Undiscounted*

Table 2: ERG exploratory analyses using updated OS models based on September 2020 data-cut and latest PAS (discount=[redacted])

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£25,431**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 1 – Kaplan-Meier estimates for TTD							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£26,761**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 2 – Updated distribution of subsequent-line therapies							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,518**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 3 – Inclusion of treatment effect waning for PFS							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£26,372**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 4 – ERG preferred analysis (ERG analysis 1 to 3 combined)							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£33,961**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; TTD - time to treatment discontinuation; PFS - progression-free survival
**undiscounted*

***Key issue 2**: No additional safety data are presented in the company submission for the CDF review*

The company's TE response[1] makes three key points:

(i) No new safety issues were identified in the final analysis of KEYNOTE-407[5]

(ii) Adverse event (AE) incidence is not a driver of the cost-effectiveness of pembrolizumab combination therapy and additional data are unlikely to change this

(iii) Drug safety is of paramount importance to the company.

As indicated in the ERG report,[1] whilst the collection of additional AE data was not included in the Terms of Engagement (ToE) for this CDF review, if these additional data had been collected, the ERG would have preferred that these were reported in the CDF-CS and incorporated into the company's economic model. However, the ERG agrees that it is unlikely that this would have a material impact on the ICER.

Key issue 3: *Committee's preferred assumptions regarding subsequent immunotherapy use do not reflect experience of KEYNOTE-407*

The company's TE response[1] states that the company undertook one-on-one interviews with ten experienced clinicians to seek information regarding the use of second-line immunotherapy (atezolizumab or pembrolizumab) following first-line chemotherapy. The clinicians unanimously agreed that patients who are eligible for single-agent immunotherapies would receive these treatments 100% of the time. Whilst the company acknowledges that this does not reflect the experience of the KEYNOTE-407 trial,[5] they state that *"no obvious methodology to adjust trial outcomes data to better reflect expected real world benefit could be identified."* The company's TE response also states that *"all potential methods of adjustment require additional assumptions and are associated with uncertainty"* and that *"MSD would assert that while imperfect, the company base case is sufficient for decision making on this point."*[1]

The ERG's agrees that the experience of the trial differs from what would now happen in usual clinical practice. As a general principle, the ERG believes that the most appropriate approach is to ensure that the economic model aligns health outcomes with the resources required to generate them. The company's approach results in a disconnect between the two, as the trial reflects outcomes in which around [redacted] of patients in the control arm received second-line chemotherapy rather than immunotherapy, yet the model applies costs associated with 100% immunotherapy use in these patients. The ERG notes that it may have been possible to apply treatment switching adjustment methods to account for this issue, but the company has not attempted this type of analysis. In the absence of statistical adjustment, this means that the company's model reflects the higher costs of immunotherapy, but does not include the additional benefits of immunotherapy over chemotherapy in these patients. The ERG therefore believes that the company's preferred ICER is likely to be an underestimate, whilst the ERG's preferred analysis is consistent with the trial but is limited as it does not fully reflect current clinical practice.

Key issue 4: *The indirect comparison for the PD-L1 tumour proportion score ≥50% subgroup presented in the company submission for the CDF review is not robust*

The company's TE response[1] highlights that the additional analyses undertaken in response to the ERG's clarification questions[7] provides sufficient clarity on this issue. The ERG generally agrees. The ERG's critique of the company's updated indirect comparison for the PD-L1 tumour proportion score (TPS) ≥50% group can be found in the ERG addendum.[3] No additional analyses have been provided by the company during TE for any of the PD-L1 subgroups.

Key issue 5: *Uncertainty concerning whether pembrolizumab combination therapy meets NICE's End-of-Life criteria*

The company's TE response[1] makes the following key points to support the argument that pembrolizumab combination therapy meets NICE's End-of-Life (EoL) criteria:

- The most recent KEYNOTE-407 data-cut[6] reports a median OS of 11.6 months for the placebo plus chemotherapy arm
- Whilst the company's model predicts a mean OS for the standard care group of 27.1 months, only 28% of patients in the ITT population treated with standard chemotherapy are predicted to remain alive at 24 months
- The OS benefit associated with pembrolizumab combination therapy reported from the final analysis[4] to the 2020 data-cut[6] was maintained (HR = 0.71) and indicates a median OS gain of 5.6 months for pembrolizumab combination compared with standard care
- The company suggests that the EoL criteria should be applied only to the ITT population, and not for separate PD-L1 subgroups
- In recent appraisals in non-small cell lung cancer (for example ID1566, nivolumab with ipilimumab and chemotherapy for untreated metastatic NSCLC), clinical experts, the ERG and the NICE team have agreed that survival is less than 24 months in the PD-L1 TPS <50% group.

Additionally, the company's TE response[1] clarifies that clinicians would use pembrolizumab as combination therapy in patients with PD-L1 TPS ≥50%, where pembrolizumab monotherapy is already available, only where there is an urgent clinical need, in line with current usage in the CDF. The company's TE response mentions that *"Either the patient has a PD-L1 TPS of 0-49% or has a PD-L1 TPS of 50-100% and requires an urgent clinical response (e.g. major impending airway obstruction) so as to justify the use of the combination of pembrolizumab carboplatin and paclitaxel rather than pembrolizumab monotherapy and this issue has been fully discussed with the patient."*[1] The ERG notes that this proposed use of pembrolizumab combination therapy in the PD-L1 TPS≥ 50% only in patients who are more clinically vulnerable is not specifically reflected in the populations included in the company's economic comparison for this subgroup. As such, the company's cost-effectiveness estimates for this subgroup may not be meaningful.

Table 3 summarises key model results based on the updated September 2020 data-cut. Overall, the ERG's views regarding whether pembrolizumab combination therapy meets the EoL criteria have not changed.[2] The ERG's updated preferred analysis suggests that mean survival in the standard care group is 2.31 years for the ITT population, whilst the incremental OS gain for pembrolizumab combination therapy is estimated to be 0.85 years (10.5 months). The use of second-line chemotherapy in some control arm patients in KEYNOTE-407 (see Key Issue 3) suggests that the mean OS for the comparator group may be an underestimate as more patients would be expected to receive second-line immunotherapy in clinical practice. The ERG considers it likely that pembrolizumab combination

therapy extends OS by more than 3 months, but there remains uncertainty about whether the short life expectancy criterion under standard care is met.

Table 3: Mean OS and proportion of patients alive at 12 and 24 months, ERG-preferred analysis, using OS models based on updated data-cut (September 2020)

Treatment group	Mean LYGs (years)	Proportion of patients alive at 12 months (%)	Proportion of patients alive at 24 months (%)
Pembrolizumab combination	[redacted]	62.9%	40.3%
Standard chemotherapy	[redacted]	50.6%	28.5%
Incremental	[redacted]	-	-

3. References

1. Merck, Sharp and Dohme Ltd. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1683]. Technical engagement response form. London, UK; 2021.
2. Tappenden P, Navega Biz A, Uttley L, Stevens JW. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]. Evidence Review Group report. Sheffield, UK; 2020.
3. Tappenden P, Navega Biz A, Uttley L, Stevens JW. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]. Evidence Review Group Report Addendum: ERG commentary on additional analyses submitted by the company. Sheffield, UK; 2020.
4. Merck, Sharp and Dohme Ltd. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]. Company's evidence submission to the National Institute for Health and Care Excellence. Hertfordshire, UK; 2020.
5. Merck, Sharp and Dohme Ltd. Clinical study report: A randomized, double-blind, Phase III study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic squamous non-small cell lung cancer subjects (KEYNOTE-407); 2018.
6. Robinson A, Vicente Baz D, Tafreshi A, Soto Parra H, Mazieres J, Cicin B*, et al.* 97O - First-line pembrolizumab plus chemotherapy for patients with advanced squamous NSCLC: 3-year follow-up from KEYNOTE-407. . *Journal of Thoracic Oncology* 2021;16 suppl 4. S748-S802.
7. Merck, Sharp and Dohme Ltd. Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]. Company's response to additional clarification questions from the ERG (April 2020). Hertfordshire, UK; 2020.

Appendix 1

Table 4: Discounted prices used in the analyses for drugs used in the model, previous prices (as in December 2020) and updated prices (May 2021 prices)

Drug	Concentration (vial volume/pack size	Price per vial/pack in model (original model, 2020)	Price per vial/pack (eMIT/ MIMS) (updated by ERG, May 2021)
paclitaxel	5.988mg/ml (16.7ml)	£9.85	£7.22 [b]
	6mg/ml (25ml)	£10.52	£12.41 [b]
	6mg/ml (50ml)	£19.68	£17.66 [b]
	6mg/ml (5ml)	£3.44	£4.41 [b]
carboplatin	10 mg/ml (15ml)	£6.35	£6.03 [b]
	10 mg/ml (45ml)	£18.73	£13.76 [b]
	10 mg/ml (5ml)	£3.18	£3.37 [b]
	10 mg/ml (60ml)	£28.24	£24.11 [b]
cisplatin	1 mg/ml (100ml)	£10.13	£8.73 [b]
	1 mg/ml (10ml)	£1.84	£5.36 [a]
	1 mg/ml (50ml)	£4.48	£5.38 [b]
docetaxel	20mg/ml (1ml)	£3.85	£3.77 [b]
	20mg/ml (4ml)	£14.74	£9.13 [b]
	20mg/ml (8ml)	£46.75	£17.95 [b]
gemcitabine	1000mg (powder – 1mg)	£7.75	£8.66 [b]
	1000mg (1)	£11.97	£10.20 [b]
	1000mg (1)	£10.18	£9.37 [b]
	200mg (powder – 1mg)	£2.97	£3.70 [b]
	200mg (1)	£3.55	£3.09 [b]
	200mg (1)	£3.29	£4.38 [b]
	2000mg (powder – 1mg)	£26.12	£324.00 [a]
	2000mg (1)	£16.32	£20.66 [b]
	2000mg (1)	£15.92	£24.19 [b]
vinorelbine	10mg/ml (1ml)	£13.75	£29.00 [a]
	10mg/ml (10 pack size)	£41.13	£52.54 [b]
	10mg/ml (5ml)	£22.58	£139.00 [a]
	10mg/ml (50ml/10 pack size)	£50.48	£157.69 [b]

Source of updated prices: a- BNF; b - eMIT (Pharmex data for the period 01/01/20 - 31/12/20, for Pharmex products shown as Generic in the period 01/07/20 - 31/12/20)

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer, CDF guidance review [ID1683]

Evidence Review Group Appendix: Updated analysis results in ERG report and addenda using updated PAS for pembrolizumab for 1st AC

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Date completed	2nd August 2021

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number NIHR130472.

1. Introduction

This appendix provides updated results including the latest confidential Patient Access Scheme (PAS) discount for pembrolizumab (discount = [redacted]) and updated prices for drugs from eMIT (see Appendix 1) for the following documents:

i. ERG Report (30th March 2020) – the results for the company's cost-effectiveness results, ERG exploratory and sensitivity analyses presented here also supersede the results from the ERG document from December 2020;
ii. ERG addendum document (1st May 2020) – the updated results for the additional analyses in the ERG addendum presented here also supersede the results from the ERG document from December 2020;
iii. ERG response to company's technical engagement (23rd July 2021) – note that these results have not been updated by the ERG and some of them present earlier versions of the PAS for comparison; these results are presented again in this document for consistency and to facilitate the overall understanding of the committee;
iv. Extra analysis requested by the Committee Chair (not previously presented) – during the PMB, the Chair requested some additional analysis to the ERG; these are presented here.

Please note that none of the analyses include confidential comparator Patient Access Scheme (cPAS) discounts for atezolizumab. The results of the analyses including cPAS discounts are presented in a separate confidential appendix.

2. ERG Report (30th March 2020)

2.1 Company's updated cost-effectiveness results

The results of the company's updated model for the ITT population and the three PD-L1 TPS subgroups are summarised in Table 1.

Table 1: Company's updated cost-effectiveness results, includes correction of errors identified by the ERG, deterministic (Table 14 of the ERG report)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ITT population							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£27,718**
Standard care	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS <1% subgroup							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,018**
Standard care	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS 1-49% subgroup							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£21,527**
Standard care	[redacted]	[redacted]	[redacted]	-	-	-	-
PD-L1 TPS ≥50% subgroup							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,563 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ITT - intention-to-treat; PD-L1 - programmed death ligand 1; TPS - tumour proportion score; SW - South West quadrant
** Undiscounted*

2.2 ERG exploratory analyses results

The results of the ERG's exploratory analyses and preferred base case analysis for the ITT population are presented in Table 2. Results of the ERG's preferred base case analysis for the PD-L1 TPS subgroups are presented in Table 3. Table 4 and Table 5 present the results of sensitivity analyses using alternative parametric models for OS within the ITT population and the PD-L1 TPS subgroups, respectively. Table 6 and Table 7 present the results of sensitivity analyses using alternative parametric models for PFS within the ITT population and the PD-L1 TPS subgroups, respectively.

Table 2: ERG preferred base case results, pembrolizumab combination therapy versus standard care, ITT population, deterministic (Table 16 of the ERG report)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£27,718**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 1 – Kaplan-Meier estimates for TTD							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,242**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG exploratory analysis 2 – Updated distribution of subsequent-line therapies							

Pembrolizumab combination	[redacted]						**£34,694**
Standard chemotherapy	[redacted]			-	-	-	-
ERG exploratory analysis 3 – Inclusion of treatment effect waning for PFS							
Pembrolizumab combination	[redacted]						**£28,348**
Standard chemotherapy	[redacted]			-	-	-	-
ERG exploratory analysis 4 – ERG preferred analysis (ERG analysis 1 to 3 combined)							
Pembrolizumab combination	[redacted]						**£36,973**
Standard chemotherapy	[redacted]			-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; TTD - time to treatment discontinuation; PFS - progression-free survival
**undiscounted*

Table 3: ERG preferred base case results, pembrolizumab combination therapy versus standard care, PD-L1 TPS subgroups (Table 17 of the ERG report)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS <1% - pembrolizumab combination therapy versus chemotherapy							
Pembrolizumab combination	[redacted]						**£47,252**
Standard chemotherapy	[redacted]			-	-	-	-
PD-L1 TPS 1-49% - pembrolizumab combination therapy versus chemotherapy							
Pembrolizumab combination	[redacted]						**£30,201**
Standard chemotherapy	[redacted]			-	-	-	-
PD-L1 TPS ≥50% - pembrolizumab combination therapy versus pembrolizumab monotherapy							
Pembrolizumab combination	[redacted]						**£15,623 (SWQ)**
Pembrolizumab monotherapy	[redacted]			-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; TTD - time to treatment discontinuation; PFS - progression-free survival; SWQ - South-West quadrant
**undiscounted*

Table 4: ERG sensitivity analysis 1 results, impact of alternative OS models, pembrolizumab combination therapy versus standard care, ITT population, deterministic (Table 18 of the ERG report)

OS model	Comparator LYGs*	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
ITT population - pembrolizumab combination therapy versus standard care					
Exponential	[redacted]				**£47,439**
Weibull	[redacted]				**£56,254**
Gompertz	[redacted]				**£75,534**
Log-normal	[redacted]				**£36,817**
Log-logistic (base case)	[redacted]				**£36,973**

Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£57,490**

*LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ITT – intention-to-treat; *undiscounted*

Table 5: ERG sensitivity analysis 1 results, impact of alternative OS models, pembrolizumab combination therapy versus standard care, PD-L1 TPS subgroups, deterministic (Table 19 of the ERG report)

OS model	Comparator LYGs*	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
PD-L1 TPS <1% - pembrolizumab combination therapy versus chemotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£67,889**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£84,396**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£130,197**
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	**£50,809**
Log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£47,252**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£181,015**
PD-L1 TPS 1-49% - pembrolizumab combination therapy versus chemotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£39,176**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£41,613**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£39,647**
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	**£29,607**
Log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£30,201**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£36,993**
PD-L1 TPS ≥50% - pembrolizumab combination therapy versus pembrolizumab monotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£120,923 (SWQ)**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£10,490 (SWQ)**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£10,996 (SWQ)**
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	**£16,292 (SWQ)**
Log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£15,623 (SWQ)**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£12,832 (SWQ)**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; OS - overall survival' PD-L1 - programmed death ligand 1; TPS - tumour proportion score; SWQ - South-West quadrant
**undiscounted*

Table 6: ERG sensitivity analysis 2 results, impact of alternative PFS models, pembrolizumab combination therapy versus standard care, ITT population, deterministic (Table 20 of the ERG report)

PFS model	Comparator survival*	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
ITT population - pembrolizumab combination therapy versus standard care					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£47,151**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£43,382**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£38,688**
Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£36,973**
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	**£37,676**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£37,815**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ITT - intention-to-treat;

**undiscounted*

Table 7: ERG sensitivity analysis 2 results, impact of alternative PFS models, pembrolizumab combination therapy versus standard care, PD-L1 TPS subgroups, deterministic (Table 21 of the ERG report)

PFS model	Comparator survival*	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
PD-L1 TPS <1% - pembrolizumab combination therapy versus chemotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£54,935**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£51,884**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£46,926**
Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£47,252**
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	**£46,611**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£46,007**
PD-L1 TPS 1-49% - pembrolizumab combination therapy versus chemotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£36,513**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£34,558**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£29,193**
Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£30,201**
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	**£30,510**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£33,241**
PD-L1 TPS ≥50% - pembrolizumab combination therapy versus pembrolizumab monotherapy					
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	**£7,884 (SWQ)**
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	**£10,313 (SWQ)**
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	**£14,350 (SWQ)**
Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	**£15,623 (SWQ)**
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	**£15,228 (SWQ)**
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	**£15,261 (SWQ)**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; OS - overall survival' PD-L1 - programmed death ligand 1; TPS - tumour proportion score; SWQ - South West quadrant
**undiscounted*

3. ERG addendum (1st May 2020)

Table 8 presents the results of the ERG preferred and alternative analyses using additional models for the ITC within PD-L1 TPS≥50% subgroup.

Table 8: ERG preferred analysis deterministic results, pembrolizumab combination therapy versus pembrolizumab monotherapy, PD-L1 TPS ≥50% subgroup (Table 2 of the ERG addendum)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG original preferred CDF-CS analysis[2]							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£15,623 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's additional analysis 1 (with re-censoring)							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£13,196 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's additional analysis 2 (failure odds transformation)†							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£14,001 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's additional analysis 4 (with population-adjustment and switching adjustment)							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£25,661 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; TTD - time to treatment discontinuation; PFS - progression-free survival; SWQ - South-West quadrant
**undiscounted*
† Treatment effect (OR) applied for 2 years based on company's indirect comparison; subsequently the OR is assumed to be 1.0. The company's other ITC analyses interpolate HRs between timepoints, assume that the 24-month HR is maintained until month 36, and that by year 5, the HR increases to 1.0

4. ERG response to company's technical engagement (23rd July 2021)

Table 9 presents the results of the company's updated base case analysis for the ITT population using the previous PAS discount for pembrolizumab and models fitted to the 2019 data-cut, and shows the individual impacts of including the updated PAS discount and other drug prices and the updated OS models based on the 2020 data-cut of KEYNOTE-407. Table 10 presents the results of the ERG's preferred analysis (originally presented in Table 16 of the ERG report[2]) using the updated OS models based on the 2020 data-cut and the latest PAS discount and drug prices.

Table 9: Company's updated cost-effectiveness results, ITT population, deterministic, using May 2019 and September 2020 data-cuts and original and latest PAS discounts (Table 1 of the ERG TE response)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case, using final analysis (data cut-off May 2019) – original PAS (ERG report, March 2020, discount=)							
Pembrolizumab combination							**£38,090**
Standard care				-	-	-	-
Company's updated base case, using final analysis (data cut-off May 2019) – updated PAS (discount=) and prices							
Pembrolizumab combination							**£27,718**
Standard care				-	-	-	-
Company's updated base case, using longer-term OS models (data cut-off September 2020, discount=)							
Pembrolizumab combination							**£25,431**
Standard care				-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ITT - intention-to-treat.
** Undiscounted*

Table 10: ERG exploratory analyses using updated OS models based on September 2020 data-cut and latest PAS (discount=) (Table 2 of the ERG TE response)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case							
Pembrolizumab combination							**£25,431**
Standard chemotherapy				-	-	-	-
ERG exploratory analysis 1 – Kaplan-Meier estimates for TTD							
Pembrolizumab combination							**£26,761**
Standard chemotherapy				-	-	-	-
ERG exploratory analysis 2 – Updated distribution of subsequent-line therapies							
Pembrolizumab combination							**£31,518**
Standard chemotherapy				-	-	-	-
ERG exploratory analysis 3 – Inclusion of treatment effect waning for PFS							
Pembrolizumab combination							**£26,372**
Standard chemotherapy				-	-	-	-
ERG exploratory analysis 4 – ERG preferred analysis (ERG analysis 1 to 3 combined)							
Pembrolizumab combination							**£33,961**

Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; TTD - time to treatment discontinuation; PFS - progression-free survival
**undiscounted*

Table 11 presents the original summary of the key model results based on the updated September 2020 data-cut, used in the discussion of End-of-Life criteria.

Table 11: Mean OS and proportion of patients alive at 12 and 24 months, ERG-preferred analysis, using OS models based on updated data-cut (September 2020, Table 3 of the ERG TE response)

Treatment group	Mean LYGs (years)	Proportion of patients alive at 12 months (%)	Proportion of patients alive at 24 months (%)
Pembrolizumab combination	[redacted]	62.9%	40.3%
Standard chemotherapy	[redacted]	50.6%	28.5%
Incremental	[redacted]	-	-

5. Additional analyses requested by the Committee Chair (not previously presented)

Table 12 summarises key model results and proportion of patients alive from the model simulations and KMs, based on the updated September 2020 data-cut.

Table 12: Mean OS and proportion of patients alive at 12 and 24 months, ERG-preferred analysis, using OS models based on updated data-cut (September 2020)

Treatment group	Model results			Data from KMs	
	Mean LYGs (years)	Proportion of patients alive at 12 months (%)	Proportion of patients alive at 24 months (%)	Proportion of patients alive at 12 months (%)	Proportion of patients alive at 24 months (%)
Pembrolizumab combination	[redacted]	62.9%	40.3%	64.7%	49.8%
Standard chemotherapy	[redacted]	50.6%	28.5%	36.0%	30.8%
Incremental	[redacted]	-	-		

Table 13 presents the results of the company's base-case model and ERG preferred analysis for the combined less than 1% and 1-49% PD-L1 TPS subgroups, based on the KEYNOTE-407 May 2019 data-cut and weighting based on the number of patients in each subgroup in the trial (48.38% with PD-L1<1% and 51.62% with PD-L1 1-49%). Please note that no additional data have been provided by the company for the latest September 2020 data-cut for any of the PD-L1 subgroups.

Table 13: ERG exploratory analyses using updated OS models based on September 2020 data-cut and latest PAS (discount=[redacted]) (Table 2 of the ERG TE response)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case - PD-L1 TPS <1%							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,018**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's updated base case - PD-L1 TPS 1-49%							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£21,527**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's updated base case - PD-L1 TPS <49% (weighted)							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£24,880**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's updated base case - PD-L1 TPS ≥50% subgroup							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,563 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG preferred analysis - PD-L1 TPS <1%							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,201**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG preferred analysis - PD-L1 TPS 1-49%							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,252**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG preferred analysis - PD-L1 TPS <49% (weighted)							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,843**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG preferred analysis - PD-L1 TPS ≥50% subgroup							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£15,623 (SWQ)**
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; TTD - time to treatment discontinuation; PFS - progression-free survival
**undiscounted*

Table 14 presents the results of the updated ERG preferred analysis for the ITT population using the updated OS models based on the 2020 data-cut of KEYNOTE-407, and shows the individual impacts

of including the updated PAS discount and other drug prices and the updated OS models based on the 2020 data-cut of KEYNOTE-407.

Table 14: Company's updated cost-effectiveness results, ITT population, deterministic, using May 2019 and September 2020 data-cuts and original and latest PAS discounts (Table 1 of the ERG TE response)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG preferred analysis, using longer-term OS models (data cut-off September 2020, discount=[redacted])							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£33,961**
Standard chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ERG preferred analysis, using longer-term OS models and TTD KMs (data cut-off September 2020, discount=[redacted])							
Pembrolizumab combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,043**
Standard care	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ITT - intention-to-treat.
** Undiscounted*

Appendix

Table 15: Discounted prices used in the analyses for drugs used in the model, previous prices (as in December 2020) and updated prices (May 2021 prices)

Drug	Concentration (vial volume/pack size	Price per vial/pack in model (original model, 2020)	Price per vial/pack (eMIT/ MIMS) (updated by ERG, May 2021)
paclitaxel	5.988mg/ml (16.7ml)	£9.85	£7.22 [b]
	6mg/ml (25ml)	£10.52	£12.41 [b]
	6mg/ml (50ml)	£19.68	£17.66 [b]
	6mg/ml (5ml)	£3.44	£4.41 [b]
carboplatin	10 mg/ml (15ml)	£6.35	£6.03 [b]
	10 mg/ml (45ml)	£18.73	£13.76 [b]
	10 mg/ml (5ml)	£3.18	£3.37 [b]
	10 mg/ml (60ml)	£28.24	£24.11 [b]
cisplatin	1 mg/ml (100ml)	£10.13	£8.73 [b]
	1 mg/ml (10ml)	£1.84	£5.36 [a]
	1 mg/ml (50ml)	£4.48	£5.38 [b]
docetaxel	20mg/ml (1ml)	£3.85	£3.77 [b]
	20mg/ml (4ml)	£14.74	£9.13 [b]
	20mg/ml (8ml)	£46.75	£17.95 [b]
gemcitabine	1000mg (powder – 1mg)	£7.75	£8.66 [b]
	1000mg (1)	£11.97	£10.20 [b]
	1000mg (1)	£10.18	£9.37 [b]
	200mg (powder – 1mg)	£2.97	£3.70 [b]
	200mg (1)	£3.55	£3.09 [b]
	200mg (1)	£3.29	£4.38 [b]
	2000mg (powder – 1mg)	£26.12	£324.00 [a]
	2000mg (1)	£16.32	£20.66 [b]
	2000mg (1)	£15.92	£24.19 [b]
vinorelbine	10mg/ml (1ml)	£13.75	£29.00 [a]
	10mg/ml (10 pack size)	£41.13	£52.54 [b]
	10mg/ml (5ml)	£22.58	£139.00 [a]
	10mg/ml (50ml/10 pack size)	£50.48	£157.69 [b]

Source of updated prices: a- BNF; b - eMIT (Pharmex data for the period 01/01/20 - 31/12/20, for Pharmex products shown as Generic in the period 01/07/20 - 31/12/20)