NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (CDF Review of TA557) [ID1584]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (CDF Review of TA557) [ID1584]

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** from Merck Sharp & Dohme
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submission** from:
   a. Roy Castle Lung Cancer Foundation
4. **Expert personal perspectives** from:
   a. Dr Samreen Ahmed, Consultant Medical Oncologist – clinical expert, nominated by the Royal College of Physicians
   b. Dr Yvonne Summers, Consultant Medical Oncologist – clinical expert, nominated by Merck, Sharp & Dohme
   c. Mrs Paula Shepherd, Lung Cancer Nurse Specialist – patient expert, nominated by Lung Cancer Nursing UK
5. **Evidence Review Group report** prepared by PenTAG
6. **Technical report sent for engagement**

Post-technical engagement documents

7. **Technical engagement response from company, Merck Sharpe & Dohme:**
   a. Technical engagement response form
   b. Technical engagement evidence supporting document
8. **Evidence Review Group critique of company response to technical engagement** prepared by PenTAG

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 TA557

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small cell lung cancer, CDF guidance review [ID1584]

Company evidence submission for committee

19th December 2019

File name	Version	Contains confidential information	Date
MSD Submission Pembrolizumab Combination [ID1584] CDF Review Without Appendices [Redacted]	**2.0**	**Yes**	**27/10/2020**

Contents

Tables and figures

A.1 Background

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

- Pembrolizumab with pemetrexed and platinum chemotherapy is recommended for use within the Cancer Drugs Fund (CDF) as an option for untreated metastatic non-small-cell lung cancer (NSCLC) in adults whose tumours have no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)-positive mutations. 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%, pemetrexed plus platinum (either carboplatin or cisplatin) with or without pemetrexed maintenance therapy was considered the standard of care.
- The key clinical evidence was taken from the phase III trial KEYNOTE-189.
    - At the most recent data cut (November 2017) during the appraisal at the CDF entry point, median overall survival for pembrolizumab combination was not reached. The median follow-up was 10.5 months (0.2 to 20.4 months)
    - The committee considered that the survival evidence was too uncertain given the immaturity of the data presented.
    - The immaturity of the trial data led to uncertainty in the extrapolation of the survival data over the time horizon of the economic model. Several plausible methods were presented to the committee which resulted in a range of cost-effectiveness estimates.
    - The committee were aware that the final data cut in the trial would be available in [redacted] and provide an additional 18 months of follow-up. The committee concluded that this could resolve the uncertainty in the survival estimates. Please note, as per the information communicated at the kick off meeting, the final analysis data cut of the trial was in May 2019.

A.2 Key committee assumptions

Table 1. Key committee assumptions as per ToE document [1]

Area	Committee preferred assumptions
Population	• Adults with untreated, metastatic, non-squamous non-small-cell lung cancer (NSCLC) whose tumours have no epidermal growth factor receptor - or anaplastic lymphoma kinase-positive mutation
Comparators	• Pemetrexed with carboplatin or cisplatin, with or without pemetrexed maintenance therapy • Chemotherapy (that is, docetaxel, gemcitabine, paclitaxel or vinorelbine as monotherapy), with carboplatin or cisplatin, with or without pemetrexed maintenance therapy). Please refer to Table 3 for more details on the comparators presented in this submission. • Pembrolizumab monotherapy (only in PD-L1-positive NSCLC if the tumour expresses at least a 50% tumour proportion score). Please refer to Table 3 for more details on the comparators presented in this submission.
Comparative evidence	• The company performed a network meta-analysis (NMA) to compare pembrolizumab combination with other chemotherapy treatments used in NHS clinical practice ○ The committee were satisfied with the methods used • The company performed an indirect treatment comparison (ITC) to compare pembrolizumab combination with pembrolizumab monotherapy for people whose tumours express PD-L1 with at least a 50% tumour proportion score.

	○ Although the effect observed was large, the 95% credible intervals around the effect were very wide and the difference was not statistically significant. ○ the company had not included data from a relevant trial, KEYNOTE-021G (an ongoing open-label phase II study comparing pembrolizumab combination with chemotherapy alone). However, committee agreed that it would not have had a substantial effect on the final effect estimates. ○ further data from KEYNOTE-189 could help to reduce the uncertainty in the overall survival estimates
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	• Proportional hazards assumption does not hold therefore the company's preferred exponential distribution is inappropriate • Committee considered there were potentially plausible curves which provided clinically plausible 5-year overall survival for the standard care arm, including the log-logistic and generalised gamma curves. • Due to immaturity of data the committee could not with any certainty, choose the most appropriate method for extrapolating overall survival data.

5-year survival rate	• A 5-year survival rate of 5% to 11% for standard care is reasonable for decision-making
Utilities	• Preference to calculate utilities using progression status with a quality-of-life decrement associated with time to death of less than 360 days applied for patients who are likely to live less than 360 days
Duration of treatment effect	• The long-term treatment effect of pembrolizumab combination after stopping treatment is plausible but its duration is uncertain • Preference to cap the benefit of pembrolizumab at 3 years and 5 years from the start of treatment
End of life	• Pembrolizumab combination compared with chemotherapy (both plus carboplatin or cisplatin) meet NICE's end-of-life criteria • Pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% tumour proportion score does not meet NICE's end-of-life criteria. This was because o modelled mean overall survival with pembrolizumab monotherapy was 28 months o The indirect treatment comparison showed no statistically significant difference in overall survival between pembrolizumab combination and pembrolizumab monotherapy
ERG's model corrections	Committee agree with the following correction from the ERG: • Coding correction (% patients utilising 2nd line therapy; half-cycle correction)

	• Adjustment for background mortality (due to the relatively short length of the trial compared to the model time horizon) • Excluding cost of PD-L1 testing (this is now routine in the NHS)

A.3 Other agreed changes

As per ToE document [1]:

- 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 2 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 pemetrexed and platinum chemotherapy, is indicated for the first line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.** The above indication was approved as a Type II variation via the EMA's Centralised Procedure. The date of the CHMP opinion was 26th July 2018 [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] months ([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	January, 2019
Data collection end date	[redacted]

A.5 Clinical effectiveness evidence

Table 3. Primary source of clinical effectiveness evidence

Study title	KEYNOTE-189
Study design	KEYNOTE-189 is a worldwide, randomised, active controlled, parallel-group, multi-centre, double-blind phase III study of the safety and efficacy of platinum plus pemetrexed chemotherapy with or without pembrolizumab for the first line treatment for patients with metastatic non-squamous non-small-cell lung cancer (NSCLC) without EGFR or ALK sensitising mutations[5].
Population	Adults with untreated, metastatic, non-squamous, NSCLC lacking EGFR and/or ALK mutation[5].
Intervention(s)	Pembrolizumab in combination with pemetrexed and platinum (carboplatin or cisplatin) chemotherapy
Comparator(s)	• Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) • with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment As discussed, and agreed at the kick off meeting, the results presented in A.6 compare the intervention to pemetrexed in combination with platinum chemotherapy. 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. The outcomes collected and presented in A.6 that address the key uncertainties encompass the intention to treat (ITT) population, in line with the data collection agreement (DCA) [6].
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.6.1- A.6.3.

A.6 Key results of the data collection

The clinical data presented in this submission are from the final analysis (FA) of the KEYNOTE-189 clinical trial, based on a data cut-off date of 20th May 2019 [7] (database lock date of [redacted]), to support this submission to NICE for the CDF guidance review of TA557 [8].
All efficacy analyses were conducted using the ITT population. At the FA data cut-off date, patients had a median duration of follow-up of 18.8 months, an additional 8.3 months compared to the submission presented at the point of CDF entry.
The key results presented below are for the ITT population, in line with the DCA, to address the key clinical uncertainty highlighted in the document[6].

A.6.1 *Overall survival – ITT Population[7]*

Table 4 and Table 5 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 0.56; 95% CI: 0.46, 0.69; p<[redacted]). Median OS in the pembrolizumab combination arm was 22.0 months compared with 10.6 months in the control (Table 4). The OS rate was higher at 6 months, 12 months and remained higher at [redacted] months ([redacted]% vs [redacted], 24 months (45.7% vs 27.3%) and [redacted] months [redacted]% vs [redacted]%) (Table 5). Figure 1 demonstrates the pembrolizumab combination curve separated from the control curve early at Month 1, with continuous separation over time.
At data cut-off, 1 of the 206 patients in the control arm continued on control treatment. Of the remaining 205 patients, 84 eligible patients with disease progression had crossed over to pembrolizumab monotherapy within the study and an additional [redacted] patients received a PD-1 antibody (pembrolizumab or nivolumab) as subsequent therapy outside of the study protocol, resulting in an overall crossover rate of [redacted]% ([redacted]). Whilst the crossover rate reported in this submission is higher than that of the original submission, the clinically meaningful OS benefit persisted.
It was not necessary to model for crossover in the current submission since second line treatment with immunotherapy is now standard of care (SoC) in the UK for patients regardless of PD-L1 expression levels.

Table 4: 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 12 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro Combo	410	258 (62.9)	[redacted]	[redacted]	22.0 (19.5, 24.5)	69.8[redacted]	0.56 (0.46, 0.69)	[redacted]
Control	206	163 (79.1)	[redacted]	[redacted]	10.6 (8.7, 13.6)	48.0[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 (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).

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

Source: [7]

Table 5: Summary of OS Rate Over Time (ITT population)

	Pembro Combo (N=410)	Control (N=206)	Total (N=616)
OS rate at 6 Months in (95% CI)†	[redacted]	[redacted]	[redacted]
OS rate at 12 Months in (95% CI)†	69.8[redacted]	48.0[redacted]	[redacted]
OS rate at 18 Months in (95% CI)†	[redacted]	[redacted]	[redacted]
OS rate at 24 Months in (95% CI)†	45.7[redacted]	27.3[redacted]	[redacted]
OS rate at 30 Months in (95% CI)†	[redacted]	[redacted]	[redacted]

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

Source: [7]

Figure 1: Kaplan-Meir Estimates of OS (ITT Population)

Source: [7]

A.6.2 *Progression Free Survival (ITT Population)* [7]

Table 6 and Table 7 present the results of the PFS analysis and Figure 2 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 0.49; 95% CI: 0.41, 0.59; p<[redacted]) (Table 6). The HR reported in the current submission is representative of a [redacted] of progression or death, with [redacted], for the pembrolizumab combination versus control, compared with the submission at point of CDF entry Median PFS for pembrolizumab combination was 9 months compared with 4.9 months for the control. The PFS benefit for the pembrolizumab combination was higher at 6 months, 12 months and remained higher at [redacted] months ([redacted]% vs [redacted]%), 24 months (22% vs 3.4%) and [redacted] months ([redacted]% vs [redacted]%) (Table 7). 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 2.

As per the KEYNOTE-189 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.

Table 6: Analysis of PFS (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS† (Months) (95% CI)	PFS Rate at Month 12 in %† (95% CI)	vs. Control	
							Hazard Ratio‡ (95% CI)‡	p-Value§
Pembro Combo	410	337 (82.2)	[redacted]	[redacted]	9.0 (8.1, 10.4)	39.4 [redacted]	0.49 (0.41, 0.59)	[redacted]
Control	206	197 (95.6)	[redacted]	[redacted]	4.9 (4.7, 5.5)	17.6 [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 (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).

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

BICR = Blinded Independent Central Review

Source: [7]

Table 7: Summary of PFS Rate Over Time Based on BICR per RECIST 1.1 (ITT population)

	Pembro Combo (N=410)	Control (N=206)	Total (N=616)
PFS rate at 6 Months in (95% CI)†	[redacted]	[redacted]	[redacted]
PFS rate at 12 Months in (95% CI)†	39.4 [redacted]	17.6 [redacted]	[redacted]
PFS rate at 18 Months in (95% CI)†	[redacted]	[redacted]	[redacted]
PFS rate at 24 Months in (95% CI)†	22.0 [redacted]	3.4 [redacted]	[redacted]
PFS rate at 30 Months in (95% CI)†	[redacted]	[redacted]	[redacted]

† From the product-limit (Kaplan-Meier) method for censored data.
BICR = Blinded Independent Central Review

Source: [7]

Figure 2: Kaplan-Meir estimates of PFS Based on BICR Assessment per RECIST 1.1 (ITT population)

Source: [7]

A.6.3 *Time on Treatment* [4]

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 8. Similarly, to the submission at the time of CDF entry, the time on treatment was longer for the pembrolizumab combination compared with the control. 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 8.

Corresponding to the original submission, more patients in the pembrolizumab combination completed all 4 cycles of carboplatin/cisplatin than in the control. Similarly, more patients in the pembrolizumab combination received ≥5 cycles of pemetrexed (i.e., pemetrexed maintenance) than in the control, regardless of the platinum administered (Table 9 and Table 10). Highlighting that patients in the pembrolizumab combination arm stay on treatment for longer compared with the control.

Table 8: Summary of Drug Exposure

	Pembro Combo (N=405)	Control (N=202)	Total (N=607)
Number of Days on Therapy (days)			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of Cycles			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
For subjects who crossed over to pembrolizumab from the control group, dose administered after crossover are excluded.			

Source: [4]

Table 9. Summary of Drug Administration by Dose Regimen (ASaT Population – Carboplatin/Pemetrexed)

Number of Administrations	Pembro Combo (N = 294)			Control (N = 145)		
	Pembrolizumab n (%)	Pemetrexed n (%)	Carboplatin n (%)	Placebo n (%)	Pemetrexed n (%)	Carboplatin n (%)
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.						

Source: [4]

Table 10. Summary of Drug Administration by Dose Regimen (ASaT Population – Cisplatin/Pemetrexed)

Number of Administrations	Pembro Combo (N = 111)			Control (N = 57)		
	Pembrolizumab n (%)	Pemetrexed n (%)	Cisplatin n (%)	Placebo n (%)	Pemetrexed n (%)	Cisplatin n (%)
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.						

Source: [4]

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 as monotherapy), with carboplatin or cisplatin, with or without pemetrexed maintenance therapy) by means of a NMA or an updated systematic literature review (SLR). The results of the NMA, in the original submission at the point of CDF entry, showed no statistically significant difference between the platinum doublet chemotherapy interventions commonly used in UK clinical practice[9]. The results showed pembrolizumab combination is beneficial for OS and PFS compared to the other platinum doublet chemotherapy interventions. Additionally, clinical expert opinion sought by the ERG, as input for the submission at CDF entry, verified the comparator in KEYNOTE-189 described by MSD as the SoC, is as such. Expert clinical advice received by the ERG acknowledged, that platinum + docetaxel, platinum + paclitaxel, and platinum + paclitaxel + bevacizumab are not commonly used in UK clinical practice [10].

Furthermore, during a previous appraisal for first line non-squamous NSCLC, it was confirmed that pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was the relevant comparator by the CDF clinical lead [11]. The statement included that other induction chemotherapies recommended in NICE's guideline on lung cancer: diagnosis and management (docetaxel, paclitaxel, gemcitabine, vinorelbine with carboplatin or

cisplatin with or without pemetrexed maintenance) are not relevant comparators because these are rarely used to treat non-squamous metastatic NSCLC in clinical practice [11]. Hence, based on the above rationale, it is not necessary nor relevant to provide an updated NMA since the comparator in the KEYNOTE-189 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.8 Incorporating collected data into the model

A.8.1 *Overall method of modelling effectiveness*

Clinical data for OS, PFS and ToT were collected during the CDF data collection period from KEYNOTE-189 (FA) to update the economic model [4, 7]. Guidance from the NICE DSU document was followed to identify the base case parametric survival models for OS and PFS extrapolation (see sections A.8.2 and A.8.3 respectively)[12]. The choice of base case parametric models was validated in terms of clinical plausibility accepted by the committee during the appraisal at the CDF entry point ("A 5-year survival rate of 5% to 11% for standard care is reasonable for decision-making "). Goodness of fit statistics along with visual inspection was used to select the parametric curves for extrapolation of ToT (see section A.8.4).

A.8.2 *Overall survival*

As per the NICE DSU guidance, the proportional hazards assumption was tested to assess whether joint or separate statistical models were more appropriate for the pembrolizumab combination and the SoC arms (see Appendix 4)[12]. Consistently with the initial submission at CDF entry point, the proportional hazard assumption does not hold, therefore, independent, separate parametric survival models were fitted to each arm's KM OS data. A range of standard parametric curves were fitted to the full KM OS data for pembrolizumab combination and for the SoC arm (Figure 3 and Figure 4).

Figure 3. Standard parametric fully fitted curves (starting week 0) for pembrolizumab combination arm – Overall Survival

Figure 4. Standard parametric fully fitted curves (starting week 0) for SoC arm – Overall Survival

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 11)

Table 11. Goodness-of-fit statistics (AIC/BIC) for pembrolizumab combination and SoC arm – Overall Survival

Pembrolizumab combination			SoC		
	ITT			ITT	
Fitted Function	AIC	BIC	Fitted Function	AIC	BIC
Exponential	3055.1	**3059.2**	Exponential	1757.1	1760.4
Weibull	**3053.4**	3061.4	Weibull	1759	1765.6
LogNormal	3073.9	3081.9	LogNormal	1747.3	1753.9
LogLogistic	3058.3	3066.3	LogLogistic	**1747.2**	**1753.8**
Gompertz	3054.5	3062.5	Gompertz	1757.1	1763.8
GenGamma	3055.4	3067.4	GenGamma	1749.1	1759.1

The loglogistic distribution provided the best statistical fit to the full OS KM data for the SoC arm and it's the fifth/fourth (AIC/BIC) better fit for the pembrolizumab combination arm. Whilst the exponential curve has the best statistical fit for the pembrolizumab combination arm, it was not deemed appropriate for selection as the proportional hazard assumption does not hold and this is consistent with the ERG's and committee's conclusion in the ToE. Additionally, the cumulative hazard plot in Appendix 4 illustrates that the change in hazard is not constant over time as there are changes in the slope around weeks 29 and 49. This change further confirms that the exponential curve is not suitable as this curve assumes constant hazard.
In terms of clinical plausibility, the exponential and the weibull distributions provided very low 5-year OS estimates (4%) for the SoC arm while the loglogistic provided a plausible estimate of 8.7% (according to ToE, 5-11% 5-year OS for the SoC is reasonable for decision making).
Finally, according to the ToE, the committee considered the loglogistic to be a potentially plausible curve and for consistency in addition to the above rationale, this curve was selected as the base case. As the second-best fitting curve for SoC and clinically plausible (5-year OS for SoC arm 9%) the lognormal was applied to both arms in a scenario analysis.

The modelled OS curves based on the approach described above are presented in Figure 5.

Figure 5. Modelled OS fully fitted parametric curves for pembrolizumab combination and SoC arm

A.8.3 *Progression Free Survival*

Consistent with the initial submission at the CDF entry point and the ToE [1], the proportional hazard assumption was found to be violated (Appendix 5). Therefore, independent, separate parametric survival models were fitted to each arm's KM PFS data. Additionally, a change in hazard was observed again, especially for the control arm. This change was more prominent early in the trial, around week 21, as in the initial submission. Therefore, a piecewise approach was deemed more appropriate to reflect the change in the hazard after this cut-off point. A range of standard parametric curves were fitted to OS data after week 21 both for pembrolizumab combination and for the SoC arm.

Figure 6. PFS KM curve vs fitted piecewise model with cut-off at 21 weeks for pembrolizumab combination arm

Figure 7. PFS KM curve vs fitted piecewise model with cut-off at 21 weeks for SoC arm

Table 12 reports the AIC/BIC statistics for the second part of the PFS piecewise curve fitting. Weibull distribution had the best fit for the pembrolizumab combination arm and for the SoC (with GenGamma having a marginally lower AIC statistic for the SoC arm) and upon visual inspection, weibull was selected as the best fitting curve to extrapolate the PFS after week 21.

Table 12. Goodness-of-fit statistics (AIC/BIC) for pembrolizumab combination and SoC arm – 21 weeks cut-off point– Progression Free Survival

Pembrolizumab combination			SoC		
	ITT			ITT	
Fitted Function	AIC	BIC	Fitted Function	AIC	BIC
Exponential	2387.9	2391.6	Exponential	856	858.6
Weibull	**2370.2**	**2377.6**	Weibull	847.5	**852.8**
LogNormal	2406.5	2413.9	LogNormal	873.5	878.8
LogLogistic	2385	2392.4	LogLogistic	866.5	871.8
Gompertz	2380.8	2388.2	Gompertz	856.2	861.5
GenGamma	2371.4	2382.5	GenGamma	**846**	854

The modelled PFS curves based on the approach described above are presented in Figure 5 and Figure 8.

Figure 8. Modelled PFS KM curves vs fitted piecewise model with cut-off at 21 weeks for pembrolizumab combination and SoC arm

A.8.4 *Time on Treatment*

As per the KEYNOTE-189 protocol [5] patients in both trial arms could discontinue at any time to due to adverse events, disease progression, inter-current illness, protocol non-compliance or investigator or patient preference. Additionally, in the case of disease progression, patients would continue on pembrolizumab post-progression if, in the investigator's treatment opinion, the patient was deriving benefit from treatment. Therefore, rather than assuming treatment terminated with disease progression, patient data corresponding to actual ToT were analysed to capture the actual utilisation and this is consistent with the submission at the CDF entry point.
Parametric functions were fitted to the KM ToT distribution for pembrolizumab combination and SoC arm to estimate treatment duration (Figure 9 and Figure 10).

Figure 9. Standard parametric curves for ToT of pembrolizumab combination

Figure 10. Standard parametric curves for ToT of SoC

The AIC/BIC statistics (Table 13) combined with visual inspection were used to select the exponential distribution for the base-case of the trial population, consistently with the submission at CDF entry point.

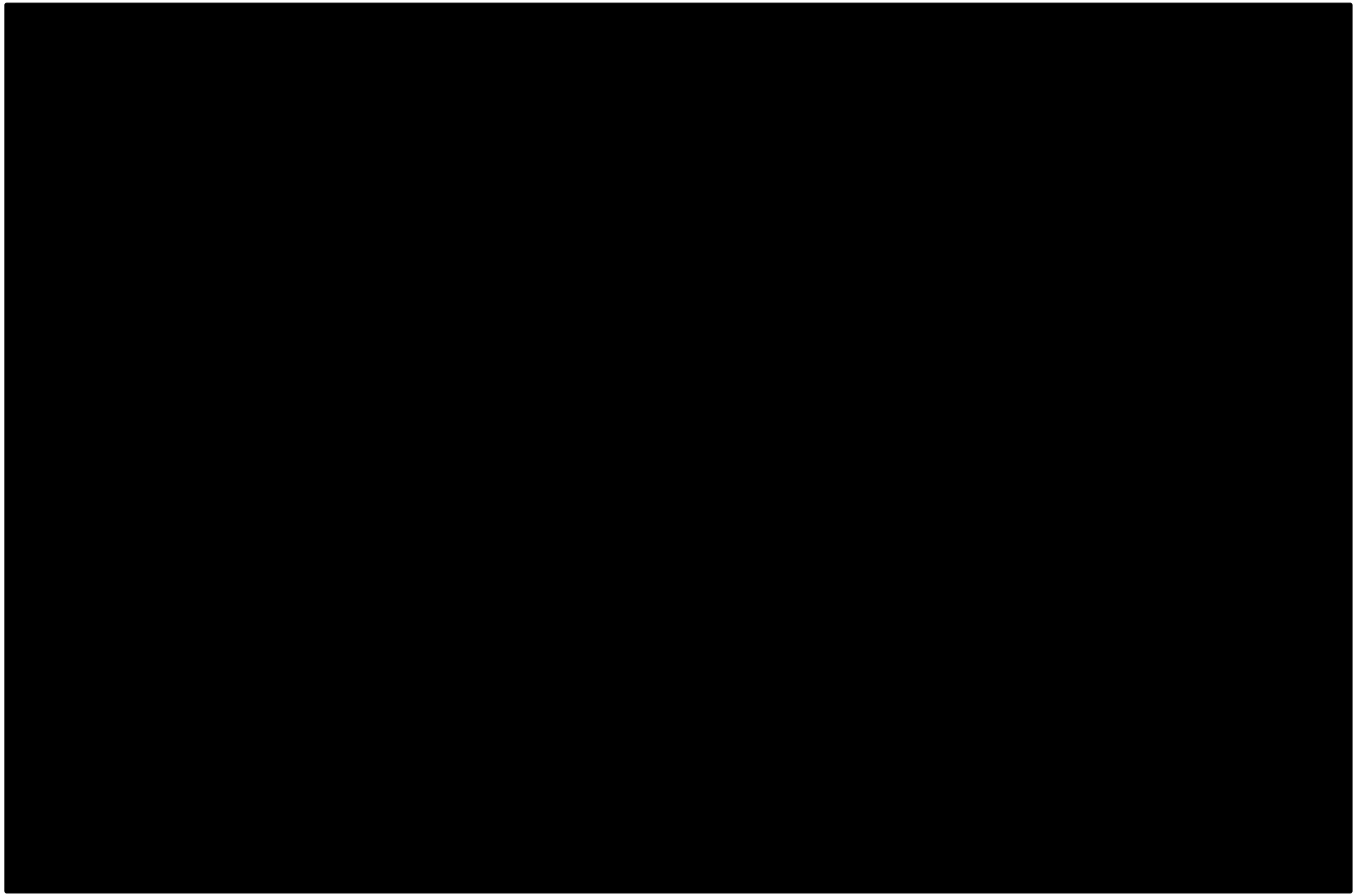
Table 13. Goodness-of-fit statistics (AIC/BIC) for pembrolizumab combination and SoC arm - ToT

Pembrolizumab combination			SoC		
	ITT			ITT	
Fitted Function	AIC	BIC	Fitted Function	AIC	BIC
Exponential	3770.2	**3774.3**	Exponential	1737.1	**1740.4**
Weibull	3772.2	3780.2	Weibull	1736.5	1743.1
LogNormal	3904.2	3912.2	LogNormal	1812.8	1819.5
LogLogistic	3837.2	3845.2	LogLogistic	1782.7	1789.3
Gompertz	3769.7	3777.7	Gompertz	1739.1	1745.7
GenGamma	**3764.8**	3776.8	GenGamma	**1731.2**	1741.2

The exponential and the gengamma had the best statistical fit for both pembrolizumab combination and SoC. For consistency with the submission at the CDF entry point, the exponential curve was selected for the extrapolation of the ToT for both arms.

Figure 11. KM data and modelled ToT based on parametric curve fitting from pembrolizumab combination arm - exponential distribution

Figure 11. KM data and modelled ToT based on parametric curve fitting from pembrolizumab combination arm - exponential distribution



A.9 Key model assumptions and inputs

Table 14. Key model assumptions and inputs

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
Overall Survival (OS) data Company submission section B.3.3.1[13] and Appendix L 'Modelling overall survival' (original submission)	Evidence from KEYNOTE-189 November 2017 data cut has been used for the overall survival in the cost-effectiveness model [13]	OS evidence from KEYNOTE-189 study, further data collection during CDF period – data cut-off May 2019[7]	As part of the DCA, further data has been collected at the FA of KEYNOTE-189. Data from this latest data cut, May 2019, has subsequently been incorporated into the cost-effectiveness model
Progression Free Survival (PFS) Company submission section B.3.3.1[13] and Appendix L 'Modelling progression free survival' (original submission)	Evidence from KEYNOTE-189 November 2017 data cut has been used for the progression-free survival in the cost-effectiveness model [13]	PFS evidence from KEYNOTE-189 study, further data collection during CDF period – data cut-off May 2019[7]	As part of the DCA, further data has been collected at the FA of KEYNOTE-189. Data from this latest data cut, May 2019, has subsequently been incorporated into the cost-effectiveness model
Time on Treatment Company submission section B.3.5.1[13] and Appendix I (original submission)	Evidence from KEYNOTE-189 November 2017 data cut has been used for the time on treatment in the cost-effectiveness model [13]	ToT evidence from KEYNOTE-189 study, further data collection during CDF period – data cut-off May 2019[4]	As part of the DCA, further data has been collected at the FA of KEYNOTE-189. Data from this latest data cut, May 2019, has subsequently been incorporated into the cost-effectiveness model
Modelling overall survival Company submission section B.3.3.1[13] and	Committee considered there were potentially plausible curves which provided clinically plausible 5-year overall	Fully fitted log-logistic parametric curve	Goodness of fit statistics and visual inspection suggests that the loglogistic is the best fitting extrapolation for the updated clinical data. Additionally, this is consistent with the ERG preferred method of extrapolation in the original submission.

Appendix L 'Modelling overall survival' (original submission)	survival for the standard care arm, including the log-logistic and generalised gamma curves		
Treatment duration Company original submission section B.3.2.2, Table 6[13]	Preference to cap the benefit of pembrolizumab at 3 years and 5 years from the start of treatment	For the base case, a 5-year cap - from treatment initiation - was implemented on the treatment duration. A scenario analysis for a 3-year cap was also implemented.	As per the FAD: "The committee considered that the duration of treatment effect is an area of uncertainty for new immunotherapies" [14].Therefore, the Committee preference was to cap at 3 years and 5 years following the start of treatment. A 3-year and 10-year cap is presented as scenario analysis. Also, as there is no evidence to suggest that the treatment effect stops after a certain time point, a lifetime treatment effect is presented as scenario analysis.
Utilities Company original submission section B.3.4.5[13]	Based on the Final Appraisal Determination, the committee preferred a combined approach for the utilities without clarifying which of the two methods explored by ERG (The ERG had included 2 scenarios which combined the time-to-death approach and progression based utility values: the first was using the PD utilities with a TTD decrement and the second one was the TTD utilities where a PD decrement was applied).	For the base case, the second ERG combined method was applied. This method is the one that used time to death (TTD), with a quality-of-life decrement associated with progressive disease (PD) applied for patients who had progressed.	Clinical expert opinion elicited from MSD and from the ERG, supported the use of the TTD approach. [As per the ERG report: "expert advice to the ERG supported the use of the TTD approach: that HRQoL is better proxied by time from death (OS) than first progression status."] [10]. However, the committee preferred the combined method based on clinical expert opinion as well, that the progression status was equally important to consider when estimating quality of life in people with NSCLC because in clinical practice, notable change in quality of life is seen when disease progresses in people on first-line treatment. Based on the above, and since the committee preferred the combined method, it is more suitable to use the second ERG combined method (ie. time to death (TTD), with a quality-of-life decrement associated with progressive disease (PD) applied for patients who progressed) as it utilizes more health states, potentially offers a better fit to patient data and also takes into consideration the progression within each state.

	The ToE document suggests that the preferred method was the first one: to calculate utilities using progression status with a quality-of-life decrement associated with time to death of less than 360 days applied for patients who are likely to live less than 360 days		
Background mortality	The committee accepted the application of background mortality in addition to the mortality cap implemented in the model	The background mortality, as it was implemented by the ERG, was not implemented in our model. However, consistently with other NSCLC submissions, the modelled OS has been capped by the survival rate for the general population	According to the ERG report, the trial "was too short to capture increasing risk of death from other causes as patients age through the time horizon" therefore a background mortality was implemented to account for the immaturity of OS data. Specifically, "the probability of dying in any given model cycle, obtained from the fitted OS distribution, has been multiplied by the probability of dying for the general population obtained from the ONS lifetables." The background mortality, as it was implemented by the ERG, was not implemented in our model. The OS data of KEYNOTE-189 capture all-cause mortality and therefore, the fully fitted extrapolated curve takes into account dying from other causes. The implementation of the background mortality could be considered as double-counting and as such it was not applied. Please note though, that the modelled OS has been capped by the survival rate for the general population. This cap is necessary, since it would be unreasonable for the modelled age-specific survival rates of metastatic NSCLC patients to be greater than those of the general population. On the base case scenario a loglogistic curve is selected. However, the cap is not triggered until year 20 (i.e. the end of the time horizon). The non-triggering of the cap during the 10-year modelled time horizon in the

			analysis base case is consistent with both lung and non-lung cancer mortality already being captured by the extrapolated OS. Thus it would be expected that mortality would remain substantively higher than a background mortality risk, as this is only one of the two components of mortality being modelled.
Patient Access Scheme (PAS)	[redacted]	[redacted]	The model was updated to reflect the PAS discount that is currently applied to the supply of pembrolizumab through routine commissioning for indications approved by NICE.

A.10 Cost-effectiveness results (deterministic)

(1) Replication of the key cost-effectiveness result(s) considered by committee to demonstrate plausible potential for cost-effectiveness at entry to the CDF;

As per the FAD [14], published after the submission at the CDF entry point, and the ToE, received by MSD subsequently[1], the committee concluded that the most plausible ICERs for pembrolizumab combination compared with chemotherapy plus carboplatin or cisplatin were highly uncertain. Committee agreed that the plausible ICERs ranged from [redacted] (lognormal curve from week 0, 5-year duration of treatment effect) to [redacted] (generalized gamma curve, 5-year duration of treatment effect) per QALY gained. Additionally, the ERG preferred a fully-fitted parameterised curve using the loglogistic distribution from week 0. This was because it was statistically the best fitting curve and had clinically plausible 5-year OS estimates of 8% for SoC. Therefore, these three ICERs that were considered by the committee, are replicated in Table **15** in response to question (1) (analyses 1a, 1b, 1c).

(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).

The original cost effectiveness model was updated to incorporate a) the data collected during the CDF data collection period and b) the ERG corrections accepted by the committee (except from the background mortality issue (see section A9 Table 14)). The updated ICERs with all inputs and parameters unchanged (except from the background mortality) are available in Table **15** (analyses 2a, 2b, 2c).

(3) Cost-effectiveness results that incorporate data collected during the CDF data collection period plus any associated changes to the company's preferred assumptions.

Table 15 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 1a: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry - **LogNormal**								
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness analysis 1b: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry - **GenGamma**								
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness analysis 1c: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry - **LogLogistic**								
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness analysis 2a: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence – **LogNormal (5-year OS for SoC: 8.7%)**								
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness analysis 2b: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence – **GenGamma (5-year OS for SoC: 8%)**								
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cost-effectiveness analysis 2c: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence – **LogLogistic (5-year OS: 8.7%)**								
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness analysis 3: New company base-case								
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

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 Table 16. The results show that the PSA results are very similar to the deterministic results.

Table 16 Updated base-case results (probabilistic) – B.3.8.1 (page 164)

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

The corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 12 and Figure 13. The cost-effectiveness acceptability curve shows that there is approximately a 16.2% 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 12. Scatterplot of probabilistic results (1,000 simulations; results discounted, with PAS) – B.5.8.1 (page 165)

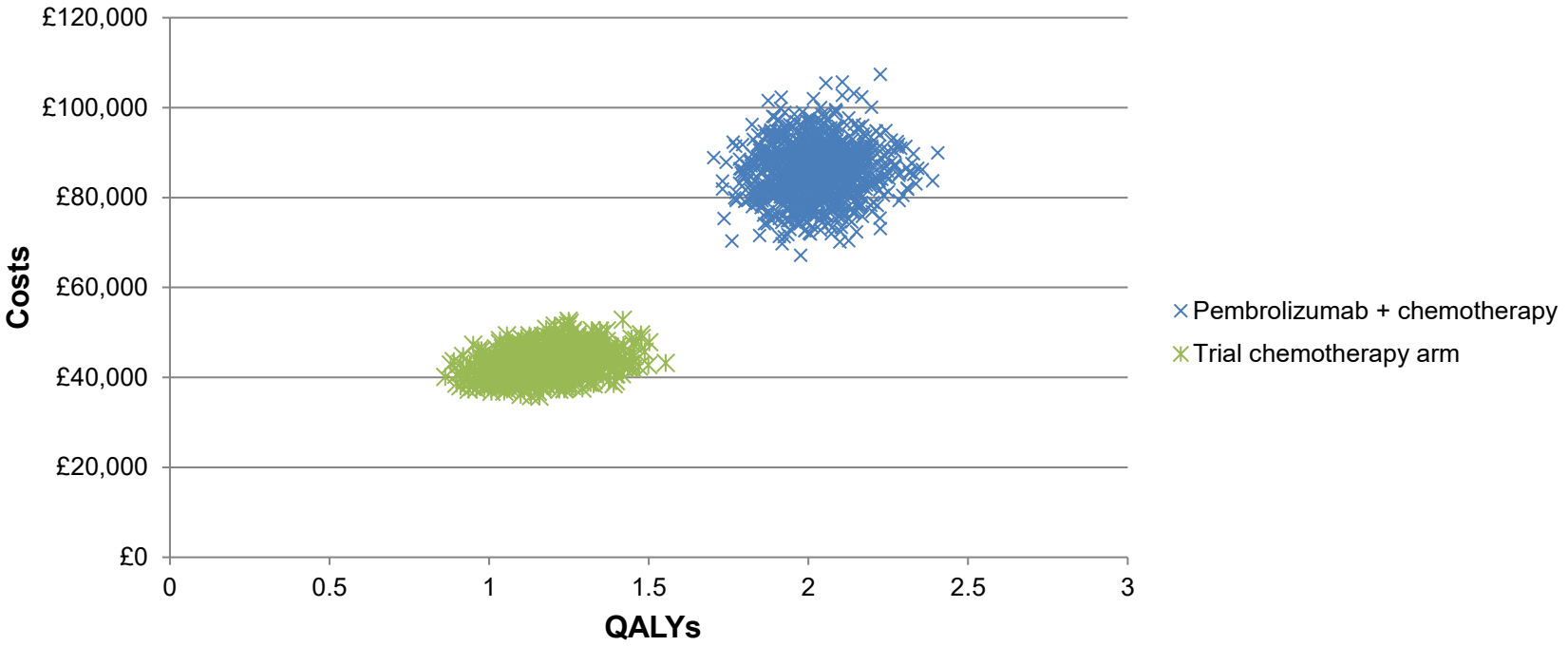
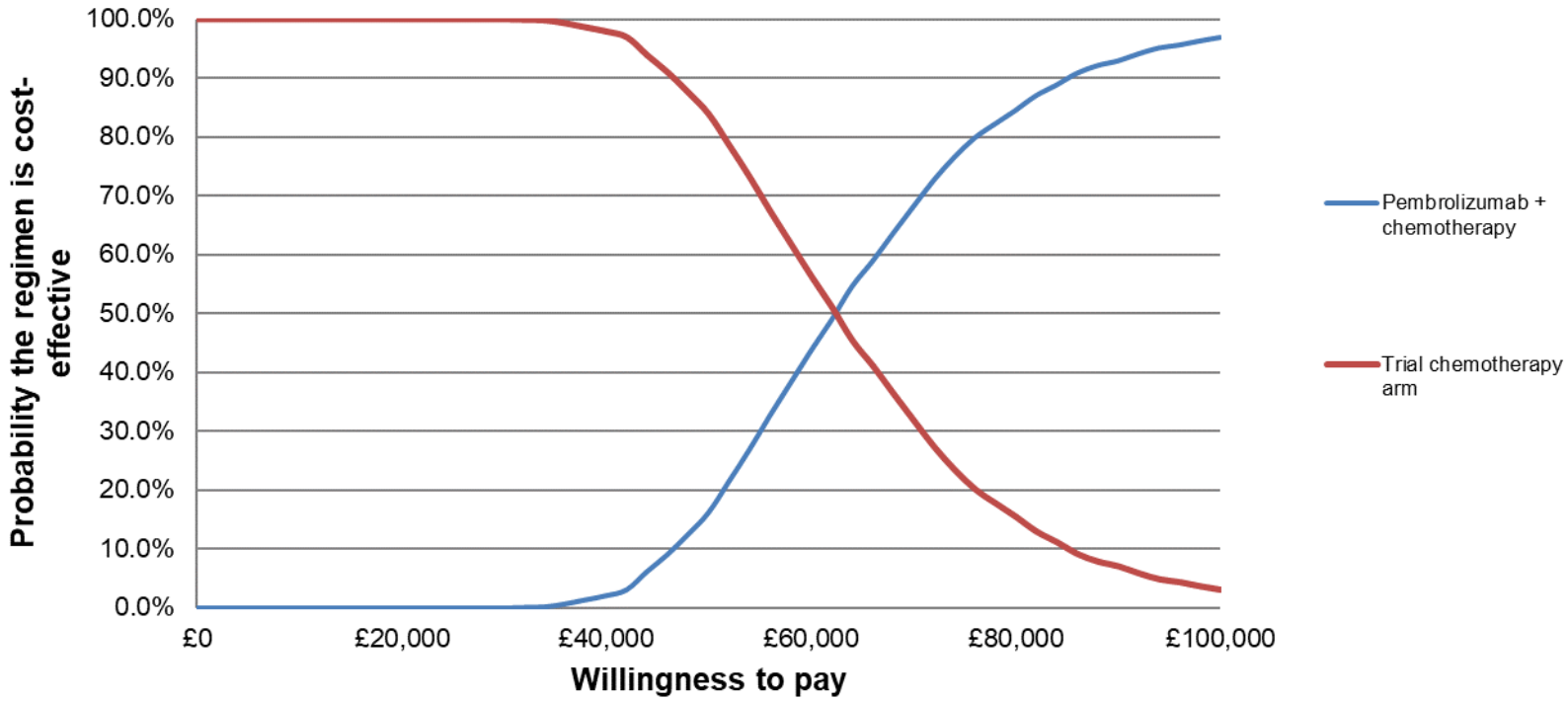


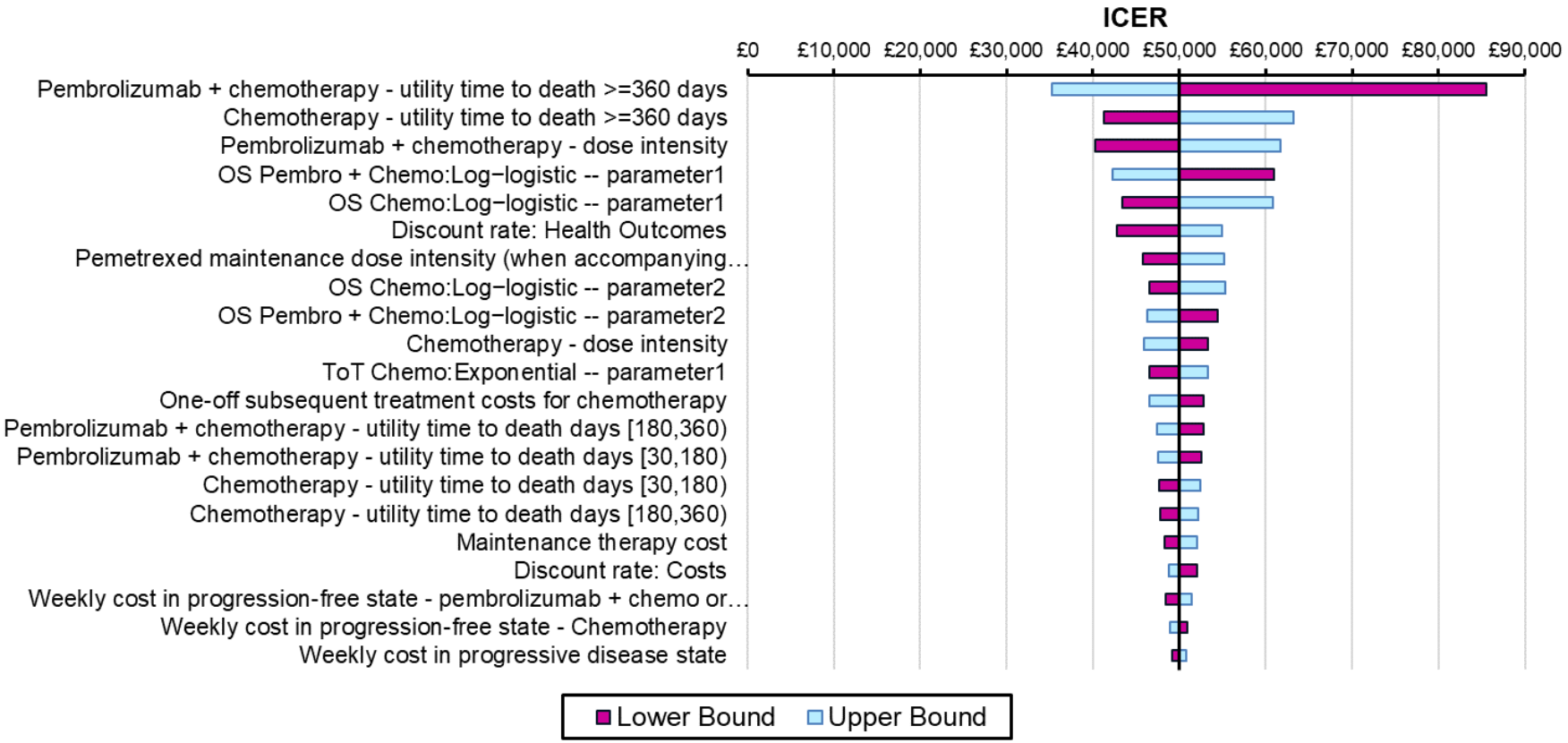
Figure 13. Cost-effectiveness acceptability curve (results discounted, with PAS)



A.12 Key sensitivity and scenario analyses

The tornado diagram depicted in Figure 14 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 time to death utilites >=360 days for both arms, dose intensity of pembrolizumab combination and the extrapolated OS curve for pembrolizumab combination arm.

Figure 14. Tornado diagram for the Incremental Cost-Effectiveness Ratio of Pembrolizumab – B.3.8.2 (page 167)



Detailed results of the OWSA are presented in Table 17. The ICER ranged from £35,258.80 /QALY to £85,540.60 /QALY for pembrolizumab versus UK SoC.

Table 17. One-Way Sensitivity Analysis Results

Parameter	Lower bound-ICER	Upper bound-ICER
Pembrolizumab + chemotherapy - utility time to death >=360 days	£85,540.60	£35,258.80
Pembrolizumab + chemotherapy - dose intensity	£40,298.18	£61,652.72
Chemotherapy - utility time to death >=360 days	£41,276.46	£63,190.43
OS Pembro + Chemo:Log−logistic -- parameter1	£60,960.26	£42,297.04
OS Chemo:Log−logistic -- parameter1	£43,384.89	£60,866.52
Discount rate: Health Outcomes	£42,740.86	£54,907.76
Pemetrexed maintenance dose intensity (when accompanying Pembrolizumab)	£45,780.30	£55,200.33
OS Chemo:Log−logistic -- parameter2	£46,540.43	£55,271.95
OS Pembro + Chemo:Log−logistic -- parameter2	£54,446.86	£46,315.08
Chemotherapy - dose intensity	£53,255.68	£45,897.28
Key: ICER, incremental cost-effectiveness ratio; Llogistic, log-logistic; OS, overall survival; PF, progression free; PP, post-progression; PFS, progression-free survival.		

Scenarios were conducted to test the uncertainty within the model and parameter uncertainty. The scenarios tested include:

- Alternative OS extrapolations
- Alternative treatment effect duration

For each scenario, the resulting ICERs are described in **Error! Reference source not found.**.

Table 18. Key scenario analyses

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			£[redacted]
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 (section A.2 table 1)	Alternative 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 for SoC arm: 9%) .	£[redacted] (+£140)
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 (section A.2 table 1)	Piecewise extrapolation at week 49	As seen at the OS log cumulative hazard plots in Appendix 4 figure 5, a change in the slope occurs at weeks 29 and 49. The piecewise method has been previously implemented for extrapolating OS in NSCLC, therefore, scenarios were tested for both cut off points. The longer cut-off point (49 weeks) from which to start extrapolation, allows for the full use of the OS KM curve and maximises the use of the trial data. Therefore a piecewise extrapolation scenario was tested were KM data were used up to week 49 and then extrapolated for the rest of the time horizon with a LogLogistic parametric extrapolation LogLogistic was selected as it provided a good statistical fit and clinically plausible outcomes (5-year OS for SoC arm: 10%	[redacted] (+£2,906)
Long term treatment effect. As per the FAD: The committee concluded that the ERG's scenarios that included a treatment effect lasting between 3 and 5years from the start of treatment were appropriate for decision making. 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	£[redacted] (+4,490) [redacted] (-£2,112)

(section A.2.Table 1, Duration of treatment effect).		of treatment effect is associated with immunotherapies due to their distinct mechanism of action[15, 16].	
Utilities: the second ERG combined method was applied. This method is the one that used time to death (TTD), with a quality-of-life decrement associated with progressive disease (PD) applied for patients who had progressed.	Alternative combined method of estimating utilities	The ToE suggested that the committee's preference was to calculate utilities using the ERG's first combined method: progression status with a quality-of-life decrement associated with time to death of less than 360 days applied for patients who are likely to live less than 360 days. Please see section A.9 Table 14	[redacted] (+£2,532)

A.13 End-of-life criteria

Table 19 End-of-life criteria – B.2.13 (page 113)

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• According to the ToE [1] "pembrolizumab combination compared with chemotherapy (both plus carboplatin or cisplatin) meet NICE's end-of-life criteria." Indeed, median OS for the SoC arm in the trial was 10.6 months (May 2019 data cut – FA) (Table 4) while the modelled median OS for the SOC arm is [redacted]months. These figures are consistent with previous studies which report median OS in patients with NSCLC between 7.5 to 11 months. The PARAMOUNT trial of pemetrexed maintenance therapy in advanced NSCLC reported median OS 13.9 months[17].

	• According to the ToE: "Pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% tumour proportion score does not meet NICE's end-of-life criteria. This was because ○ modelled mean overall survival with pembrolizumab monotherapy was 28 months ○ The indirect treatment comparison showed no statistically significant difference in overall survival between pembrolizumab combination and pembrolizumab monotherapy" As per section A.6 the ITT population is presented. However, in terms of the high expressor subgroups, the most recent update of KEYNOTE-024 (untreated, metastatic NSCLC, high expressors, squamous and non-squamous histology) reported median OS 30 months with pembrolizumab monotherapy and14.2 months with chemotherapy [18]. In conclusion, pembrolizumab combination meets the end of life criteria.
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-189 was 11.4 months (Table 4) while the modelled gain in OS was [redacted] months ([redacted] 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

Pembrolizumab for adults with untreated, metastatic, non-squamous NSCLC lacking EGFR and/or ALK mutation meets NICE's criteria to be considered as a life extending treatment at the end of life. During the original appraisal (TA557)[8], the committee considered that pembrolizumab combination has plausible potential to be cost-effective, and that further data collection would reduce the uncertainty around OS therefore, a recommendation was made as an option for use in the CDF. To adhere to the commitment made in the DCA which formed part of the Managed

Access Agreement for (TA557) [6], an additional data-cut, dated May 2019, has been conducted from the KEYNOTE-189 trial data [7], which is the FA. As agreed with NICE, only OS, PFS and ToT data has been updated – all other data variables remain as per the original submission [6]. This data, which forms the basis of this CDF guidance review, provides an additional 8.3 months of follow-up data beyond the data-cut provided during the original appraisal at the point of CDF entry.

The results from the FA of KEYNOTE-189 provide unequivocal evidence that treatment with pembrolizumab combination provides clinically meaningful benefit compared to the SOC. The OS and PFS analysis reported from the May 2019 data-cut shows that pembrolizumab combination substantially reduces the risk of death by 44% and reduces risk of disease progression or death by 51% compared with the SoC in patients with untreated, metastatic, non-squamous NSCLC lacking EGFR and/or ALK mutation[7]. The results are not only consistent with previous data-cuts, but also demonstrates a continued improvement in OS and PFS over the time with pembrolizumab combination when compared to SoC.

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. QALYs were estimated by considering a combined method of time to death and progression-based utilities derived from EQ-5D data collected in KEYNOTE-189 trial. Clinical and economic outcomes were projected over a 20-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-189 data [7], following NICE DSU guidance[12]. With the incorporation of the updated OS, PFS and ToT data from the May 2019 data-cut data-cut, the model estimates that patients treated with pembrolizumab combination gain [redacted] additional QALYS compared to UK SoC. The ICER when comparing pembrolizumab combination to UK SoC is [redacted] (PAS included). The probability of pembrolizumab being the most cost-effective treatment at a threshold of £50,000 per QALY gained is 16.2%. The results demonstrate that pembrolizumab, 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 for the treatment of metastatic, non-squamous non-small-cell lung cancer lung cancer

Results from multiple sensitivity analyses showed the ICER to be consistently below £50,000 per QALY (discounted, with the PAS). The inputs that mostly effect the cost-effectiveness analyses results were the discount rates for health outcomes, the dose intensity, and extrapolation of OS. The sensitivity analyses conducted demonstrated that the cost-effectiveness of pembrolizumab is resilient to the different sources of uncertainty assessed.

The base-case analyses cover the all-comers population, given that KEYNOTE-189 and the current NICE guidance is reflective of an all-comers population. In conclusion, pembrolizumab offers a cost-effective option, representing value for money for the NHS, with an innovative mode of action and demonstrable survival benefit in patients with metastatic, non-squamous non-small-cell lung cancer lung cancer.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lung cancer (non-small-cell, untreated) - pembrolizumab (with pemetrexed and chemotherapy) (CDF Review of TA557)

Clarification questions

January 2020

File name	Version	Contains confidential information	Date
ID1584 pembrolizumab clarification letter from ERG [REDACTED]	3	Yes	27/10/2020

Notes for company

Highlighting in the template

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

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

A.1 Section A: Clarification on effectiveness data

A.1.1 *Clarification on omission of comparator*

A1. Priority: Please can the company provide justification as to why evidence has not been provided to compare the effectiveness of pembrolizumab combination with pembrolizumab monotherapy in the PD-L1-positive non-small-cell lung cancer (NSCLC) group where the tumour expresses ≥50% on the tumour proportion score? If the company does not consider this a subgroup of relevance, then in addition to providing justification for this, please provide a comparison of pembrolizumab combination therapy with standard of care (SoC) (consisting of pemetrexed with carboplatin or cisplatin) for the subgroup where pembrolizumab monotherapy is not recommended (i.e. those with a tumour expression of <50%).

Evidence was not provided to compare the effectiveness of pembrolizumab combination with pembrolizumab monotherapy in the PD-L1 TPS ≥50% subgroup since, as per the discussion at the kick off meeting, this key uncertainty was introduced in the ToE document [1] and was not in accordance with the signed MAA document. Hence, the results of the overall population were presented to address the key clinical uncertainty as agreed in the MAA[2].

CLINICAL EFFECTIVENESS RESULTS FOR THE COMPARISON PEMBROLIZUMAB COMBINATION VERSUS PEMBROLIZUMAB MONOTHERAPY

The indirect treatment comparison (ITC) which compares pembrolizumab combination with pembrolizumab monotherapy in the PD-L1 TPS ≥50% subgroup is presented below, as requested. Please note that this is an update of the ITC which was presented in the submission at the CDF entry point and used for the base case comparison of pembrolizumab combination versus pembrolizumab monotherapy (PD-L1 TPS ≥50% subgroup). Apart from updated data for KEYNOTE-189, this ITC also includes cohort G from KEYNOTE-21 for the pembrolizumab combination arm because, as per the FAD, " *The committee considered that individual patient data from KEYNOTE-021G should have been included in the analysis because they were relevant to the comparison.".* Additionally, since the time of the submission at the CDF entry point, data from KEYNOTE-042 became available and these were also included in this ITC (in the pembrolizumab monotherapy arm) due to their relevance to the population.

Pembrolizumab Combination versus Pembrolizumab Monotherapy Indirect Treatment Comparison (ITC) [3]

Overview

To estimate the treatment difference of pembrolizumab combination and pembrolizumab monotherapy, an ITC of overall survival (OS) and progression free survival (PFS) outcomes was conducted, based on data from KEYNOTE-189, KEYNOTE-021 Cohort G, KEYNOTE-042 and KEYNOTE-024.

The ITT population from the trials were used for the analysis. To provide meaningful comparison, patients with non-squamous and strong PD-L1 expression levels (tumour proportion score (TPS) ≥50%) pre-assigned to carboplatin-pemetrexed or cisplatin-pemetrexed were selected from KEYNOTE-189 + KEYNOTE-021G vs. KEYNOTE-042 + KEYNOTE-024. Treatment arms and population selection are summarised in Table 1. The ITC was performed using the Bucher method after adjusting/weighting the populations in each treatment arm using the Inverse Probability of Treatment Weighting (IPTW) method to balance out the covariates known to influence treatment outcomes.

There was a benefit in OS and PFS for pembrolizumab combination over pembrolizumab monotherapy in metastatic, non-squamous NSCLC subjects pre-assigned to carboplatin + pemetrexed or cisplatin + pemetrexed. Whilst confidence intervals around the estimated hazard ratios were generally wide due to the limited sample sizes in the individual trials, as from each trial only non-squamous NSCLC subjects pre-assigned to carboplatin + pemetrexed or cisplatin + pemetrexed were included in the indirect treatment comparisons. This subsetting was done to match the patient population in trials and have a common control arm as anchor in the indirect treatment comparisons.

Table 1. Summary of ITC patient selection (Ref)

KEYNOTE Trial	Treatment arms	Population Selection	Data Cut-Off Date
KEYNOTE-189	- Pembrolizumab + Chemotherapy[a] - Chemotherapy[a]	Strong PD-L1 subjects (TPS ≥50%)[b]	20th May 2019
KENOTE-021G	- Pembrolizumab + Chemotherapy[a] - Chemotherapy[a]	Strong PD-L1 subjects (TPS ≥50%)[b]	31st May 2017
KEYNOTE-042	- Pembrolizumab - Chemotherapy[a]	Non-squamous histology subjects[c] Strong PD-L1 subjects (TPS ≥50%) [b]	4th September 2018
KENOTE-024	- Pembrolizumab - Chemotherapy[a]	Non-squamous histology subjects[c]	OS 10th July 2017 PFS 9th May 2016
a: Pemetrexed and Carboplatin or Pemetrexed and Cisplatin for KEYNOTE-189 and KEYNOTE-024 and Pemetrexed and Carboplatin for KEYNOTE-042 and KEYNOTE-021G b: KEYNOTE-024 contains TPS ≥50% subjects only; patients with the same criterion are selected from KEYNOTE-189, KEYNOTE-021G and KEYNOTE -042 c: KEYNOTE-189 and KEYNOTE-021G contain non-squamous subjects only; patients with the same criterion are selected from KEYNOTE-042 and KEYNOTE-024			

In addition, the following data exclusions were also performed to ensure complete similarity between the different study populations:

- Stage 3 patients from KEYNOTE-042 and KEYNOTE-021G were excluded as in KEYNOTE-189 and KEYNOTE-024 patients with the same criterion were excluded;
- Patients with untreated brain metastases were excluded from KEYNOTE-189 as KEYNOTE-042, KEYNOTE-024 and KEYNOTE-021G had excluded patients with the same criterion.

Methods

The relative treatment effect of pembrolizumab combination vs pembrolizumab monotherapy was measured by a Hazard Ratio (HR) under the proportional hazard assumption. The indirect treatment comparison was performed using the Bucher method after adjusting populations and treatment arms using IPTW.

The methodology can be summarized in two steps:

• The analysis of each individual trial based on the adjusted population resulting in an estimate of the treatment effect (log HR) and its standard error. A description of the methods used to estimate the treatment effects in each individual trial is given below

• The indirect treatment comparison using Bucher method as detailed below.

Step 1: Analyses of individual trials based on the adjusted population

The populations in both trials and four treatment arms were adjusted by balancing out the covariates known to influence the outcome.

The IPTW methodology was applied to calculate weights on patient level data. The predicted probability of receiving a specific treatment for each subject, referred as propensity score, was calculated using a multinomial logistic regression to balance out the 4 treatment arms. The four treatment arms considered for the multinomial logistic regression were:

1. KEYNOTE-189 + KEYNOTE-021G – pembrolizumab + chemotherapy arm

2. KEYNOTE-189 + KEYNOTE-021G – chemotherapy arm

3. KEYNOTE-042 + KEYNOTE-024 – pembrolizumab arm

4. KEYNOTE-042 + KEYNOTE-024 – chemotherapy arm

The covariates of interest that were used to predict the probability of treatment in the logistic model included the stratification factors of individual studies and additional other effect modifiers. Specifically, the following covariates were considered: ECOG PS (0 vs. 1), smoking status (never vs. former / current), age, gender, baseline tumour size. Hence, the inverse of the propensity score calculated for each subject represented the weight for that subject. The resulting weights were also stabilised 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, as population selection based on the proposed criteria (non-squamous, TPS≥50%, control arms) might itself induce an imbalance within each trial.

The quality of the balancing was checked by summarizing the covariates considered per study and per treatment arm (N and percentages; or mean) before and after weighting. By reporting the standardised absolute difference in mean for continuous covariate and in proportion for different categories of the baseline factors. The maximum standardised 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 standardised absolute differences are equal for the 2 categories of a binary baseline variable. Standardised absolute differences before and after weighting are provided.

Afterwards, endpoints were analyzed for each of the two studies separately using a weighted Cox Proportional Hazard model in which the weights were obtained by the IPTW described above. In each trial, the weight was used in the Cox model (proc phreg) with ‘normalize’ option, in order to maintain the statistical power of the actual sample size. The robust sandwich estimate of the covariance matrix was selected using the option ‘covs (aggregate)’.

Step 2: Indirect treatment comparison using Bucher method

For each endpoint the Bucher method uses the estimated treatment effects and standard errors of the individual trials resulting from the weighted Cox models. The

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

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

With:

- $TE_{PC\text{-}C}$ being the treatment effect of pembrolizumab combo vs control (KEYNOTE-189+ KEYNOTE-021G)
- $TE_{PM\text{-}C}$ being the treatment effect of pembrolizumab mono vs control (KEYNOTE-042+ KEYNOTE-024)
- $TE_{PC\text{-}PM}$ being the treatment effect of pembrolizumab combo vs pembrolizumab mono by means of the indirect comparison via the control arms.

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

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:

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

The 95%CI was then calculated as follows:

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

The test of presence of treatment effect was based on the Z-statistic provided by:

$$Z = TE_{PC\text{-}PM}/SE_{PC\text{-}PM}$$

Under the null hypothesis of no treatment effect, the Z-statistic follows a standard normal distribution. The two-sided p-value was calculated from the above Z-statistic test.

All the endpoints of interest in this report are time to event, the treatment effect in each trial was estimated by the log hazard ratio and corresponding standard error. The log hazard ratio is the original estimate from the Cox model (i.e. before transforming to hazard ratio by exponentiation).

Presentation of results

A total of [redacted] subjects with non-squamous histology and strong PD-L1 (TPS≥50%) were selected in the study KEYNOTE-189 + KEYNOTE-021G, resulting in [redacted] subjects in pembrolizumab combination arm and [redacted] in the chemotherapy arm.

A total of [redacted] subjects with non-squamous histology and strong PD-L1 were selected from study KEYNOTE-024 + KEYNOTE-042, including [redacted] subjects in the pembrolizumab monotherapy arm and [redacted] subjects in the chemotherapy arm.

Table 2 summarises the weight calculated for each subject and used to balance out the subject characteristics across the 4 treatment arms. The weights range from [redacted] to [redacted] with a median of [redacted]. Overall, the range of weights was highest for subjects in the chemotherapy arm of KEYNOTE-189 + KEYNOTE-021G (i.e., [redacted] to [redacted]).Table 3 and Table 4 show the baseline characteristics before and after weighting, respectively. Imbalance in distribution was observed for ECOG (0 vs. 1 or 2) and smoker (never, former / current). These subjects' characterises were better balanced across the 4 arms after weighting.

Table 2. Subject Characteristics - Studies 189+021G and 042+024 Inverse Probability of Treatment Weight (Intention-to-Treat Population, TPS ≥ 50%)

	Study 189[a] + 021G[b]		Study 042[c] + 024 [d]		
	Pembrolizumab + Chemotherapy	Chemotherapy	Pembrolizumab	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: 20MAY2019
b: Database Cutoff Date: 31MAY2017
c: Database Cutoff Date: 04SEP2018
d: Database Cutoff Date: 10JUL2017

Table 3. Subject Characteristics - Studies 189+021G and 042+024 Before Weighting (Intention-to-Treat Population, TPS ≥ 50%)

	Before Weighting			
	Study 189[a] + 021G[b]		Study 042[c] + 024[d]	
	Pembrolizumab + Chemotherapy (N=140)	Chemotherapy (N=80)	Pembrolizumab (N=249)	Chemotherapy (N=251)
Age (mean 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: 20MAY2019
b: Database Cutoff Date: 31MAY2017
c: Database Cutoff Date: 04SEP2018
d: Database Cutoff Date: 10JUL2017
ECOG = European Cooperative Oncology Group.

Table 4. Subject Characteristics - Studies 189+021G and 042+024 After Weighting (Intention-to-Treat Population, TPS ≥ 50%)

	After Weighting			
	Study 189[a] + 021G[b]		Study 042[c] + 024[d]	
	Pembrolizumab + Chemotherapy (N=140)	Chemotherapy (N=80)	Pembrolizumab (N=249)	Chemotherapy (N=251)
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: 20MAY2019
b: Database Cutoff Date: 31MAY2017
c: Database Cutoff Date: 04SEP2018
d: Database Cutoff Date: 10JUL2017
ECOG = European Cooperative Oncology Group.

Overall Survival

Figure 1 and Figure 2 describe the Kaplan-Meier curves for overall survival in studies KEYNOTE-189 + KEYNOTE-021G, and KEYNOTE-042 + KEYNOTE-024 respectively. Whilst the Kaplan-Meier curves of the 4 treatment arms are displayed together in Figure 3. The Kaplan-Meier curves are based on the data as observed, prior to any population adjustment (i.e. prior to weighting approach).

Table 5 presents the results of the indirect treatment comparison of pembrolizumab combination vs. pembrolizumab monotherapy on OS after population adjustment/weighting. As with the ITC presented in the submission at the point of CDF entry, the ITC shows a numerical benefit in OS for pembrolizumab combination vs pembrolizumab monotherapy; however, the difference was not statistically significant; the HR for the comparison is [redacted]

Figure 1. Kaplan-Meier of Overall Survival ITT Population, TPS ≥ 50% (Study KEYNOTE-189 + KEYNOTE-021G)

Figure 2. Kaplan-Meier of Overall Survival ITT Population, TPS ≥ 50% (Study KEYNOTE-042+ KEYNOTE-024)

Figure 3. Kaplan-Meier of Overall Survival - Studies KEYNOTE-189 + KEYNOTE- 021G and KEYNOTE-042 + KEYNOTE-024 Unadjusted Survival Curves (ITT Population, TPS ≥ 50%)

Table 5. Indirect Treatment Comparison Overall Survival - Studies KEYNOTE-189 + KEYNOTE-021G and KEYNOTE-042 + KEYNOTE-024

Indirect Treatment Comparison (ITC)	Pembrolizumab + Chemotherapy[a]			Pembrolizumab Monotherapy			Chemotherapy[a]					
Endpoint	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95 %-CI]	Hazard Ratio[d,g] [95 %-CI]	ITC Hazard Ratio[e] [95 %-CI]	p-Value[f]
Overall Survival - population adjusted by weighting												
Study: P189[h] + P021G[i]	[redacted]											
Study: P042[j] + P024[k]	[redacted]											

a: Pemetrexed and Carboplatin or Pemetrexed and Cisplatin for P189 and P024 and Pemetrexed and Carboplatin for P042 and P021G

b: Number of patients: intention-to-treat, non-squamous subjects pre-assigned to Carboplatin + Pemetrexed or Cisplatin + Pemetrexed with TPS ≥ 50%

c: From product-limit (Kaplan-Meier) method

d: Based on Cox regression model with treatment, platinum chemotherapy (Cisplatin vs. Carboplatin) and smoking status (never vs. former/current) as covariates and stratified by study (P189 vs. P021G) for P189+P021G, and with treatment, ECOG PS (0 vs. 1) and geographic region (East Asia vs. non-East Asia) as covariates and stratified by study (P042 vs. P024) for P042+P024

e: Bucher methodology using separate study results (estimate and its standard error) with a common control arm to perform indirect comparison of effect of pembrolizumab combination (P189+P021G) vs monotherapy (P042+P024)

f: Two-sided p-value calculated from the test statistic associated with the ITC estimate and its standard error

g: The inverse probability of treatment weighting (IPTW) method using a multinomial logistic regression was performed with covariates: smoking status (never vs. former/current), ECOG PS (0 vs. 1), age, gender and baseline tumor size. The derived weights were used in the Cox model to adjust for population imbalance across studies and treatment arms.

h: Database Cutoff Date: 20MAY2019

i: Database Cutoff Date: 31MAY2017

j: Database Cutoff Date: 04SEP2018

k: Database Cutoff Date: 10JUL2017

CI: Confidence Interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ITC: Indirect Treatment Comparison; TPS: Tumor Proportion Score.

Progression Free Survival

XXXXXXX Figure **4** and Figure 5 describe the Kaplan-Meier curves for PFS in studies KEYNOTE-189 + KEYNOTE-021G, and KEYNOTE-042 + KEYNOTE-024 respectively. Whilst the Kaplan-Meier curves of the 4 treatment arms are displayed together in Figure 6. The Kaplan-Meier curves are based on the data as observed, prior to any population adjustment (i.e. prior to weighting approach).

Table ***6*** presents the results of the indirect treatment comparison of pembrolizumab combination vs. pembrolizumab monotherapy on PFS after population adjustment/weighting. The ITC analysis shows a statistically significant benefit in

PFS for pembrolizumab combination vs pembrolizumab monotherapy [redacted]

Figure 4. Kaplan-Meier of Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 ITT Population, TPS ≥ 50% (Study KEYNOTE-189 + KEYNOTE-021G)

Figure 5. Kaplan-Meier of Progression-Free-Survival Based on BICR Assessment per RECIST 1.1 TT Population, TPS ≥ 50% (Study KEYNOTE-042 + KEYNOTE- 024)

Figure 6. Kaplan-Meier of Progression-Free Survival - Studies KEYNOTE-189 + KEYNOTE-021G and KEYNOTE-042 + KEYNOTE-024 Unadjusted Survival Curves (ITT Population, TPS ≥ 50%)

Table 6. Indirect Treatment Comparison Progression-Free Survival - Studies KEYNOTE-189 + KEYNOTE-021G and KEYNOTE-042 + KEYNOTE-024 Population Adjusted Analysis (Intention-to-Treat Population, TPS ≥ 50%)

Indirect Treatment Comparison (ITC)	Pembrolizumab + Chemotherapy[a]			Pembrolizumab Monotherapy			Chemotherapy[a]					
Endpoint	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95 %-CI]	N[b]	Patients with Event n (%)	Median Survival Time[c] in Months [95 %-CI]	Hazard Ratio[d,g] [95 %-CI]	ITC Hazard Ratio[e] [95 %-CI]	p-Value[f]
Progression Free Survival - population adjusted by weighting												
Study: P189[h] + P021G[i]	[redacted]											
Study: P042[j] + P024[k]	[redacted]											

a: Pemetrexed and Carboplatin or Pemetrexed and Cisplatin for P189 and P024 and Pemetrexed and Carboplatin for P042 and P021G

b: Number of patients: intention-to-treat, non-squamous subjects pre-assigned to Carboplatin + Pemetrexed or Cisplatin + Pemetrexed with TPS ≥ 50%

c: From product-limit (Kaplan-Meier) method

d: Based on Cox regression model with treatment, platinum chemotherapy (Cisplatin vs. Carboplatin) and smoking status (never vs. former/current) as covariates and stratified by study (P189 vs. P021G) for P189+P021G, and with treatment, ECOG PS (0 vs. 1) and geographic region (East Asia vs. non-East Asia) as covariates and stratified by study (P042 vs. P024) for P042+P024

e: Bucher methodology using separate study results (estimate and its standard error) with a common control arm to perform indirect comparison of effect of pembrolizumab combination (P189+P021G) vs monotherapy (P042+P024)

f: Two-sided p-value calculated from the test statistic associated with the ITC estimate and its standard error

g: The inverse probability of treatment weighting (IPTW) method using a multinomial logistic regression was performed with covariates: smoking status (never vs. former/current), ECOG PS (0 vs. 1), age, gender and baseline tumor size. The derived weights were used in the Cox model to adjust for population imbalance across studies and treatment arms.

h: Database Cutoff Date: 20MAY2019

i: Database Cutoff Date: 31MAY2017

j: Database Cutoff Date: 04SEP2018

k: Database Cutoff Date: 09MAY2016

CI: Confidence Interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ITC: Indirect Treatment Comparison; TPS: Tumor Proportion Score.

COST- EFFECTIVENESS RESULTS FOR THE COMPARISON PEMBROLIZUMAB COMBINATION VERSUS PEMBROLIZUMAB MONOTHERAPY

The evidence (OS and PFS) for the cost effectiveness comparison of pembrolizumab combination versus pembrolizumab monotherapy derived from the ITC described above. Four trials were included: KEYNOTE-189 + KEYNOTE-021G vs. KEYNOTE-042 + KEYNOTE-024. The ToT for pembrolizumab monotherapy was derived from KEYNOTE 024 consistently with the original submission. The rest of the parameters in the model were assumed same as for the ITT population base case.

Table 7. Base case result of sub-population comparison for patients with TPS>=50%, pembrolizumab combination versus pembrolizumab monotherapy

Comparators	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pembrolizumab combination C	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A.1.2 *Requests for data and analysis outputs*

A2. Priority: Please can the company provide Kaplan-Meier curves for the outcome of 'time on treatment' (ToT) based on the latest data-cut of the KEYNOTE-189 trial?

The KM curves for the Time on Treatment (ToT) based on the latest data cut of KEYNOTE-189 are illustrated in Figure 7 below:

Figure 7 Kaplan-Meier Curves of Time on Treatment (All-Subjects-as-Treated Population)

A3. Table 4 and Table 5 in the company submission provide hazard ratios (HRs) of pembrolizumab combination therapy compared to the control arm based on data from KEYNOTE-189. Please can the company provide the same information with data from the first interim analysis (data cut-off date: 08 Nov 2017) of KEYNOTE-189 "IA1".

Table 8. Analysis of OS (ITT Population IA1)

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	410	[redacted]	[redacted]	[redacted]	Not Reached (., .)	[redacted]	0.49 (0.38, 0.64)	<0.00001
Control	206	[redacted]	[redacted]	[redacted]	11.3 (8.7, 15.1)	[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 (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
Database Cutoff Date: 08NOV2017

Table 9. Summary of OS Rate Over Time (ITT Population IA1)

	Pembro Combo (N=410)	Control (N=206)	Total (N=616)
OS rate at 6 Months in (95% CI)†	[redacted]	[redacted]	[redacted]
OS rate at 9 Months in (95% CI)†	[redacted]	[redacted]	[redacted]
OS rate at 12 Months in (95% CI)†	69.2 (64.1, 73.8)	49.4 (42.1, 56.2)	62.5 (58.3, 66.5)

† From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 08NOV2017

Table 10. Analysis of PFS based on BICR assessment per RECIST 1.1 (ITT Population IA1)

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	410	[redacted]	[redacted]	[redacted]	8.8 (7.6, 9.2)	[redacted]	0.52 (0.43, 0.64)	<0.00001
Control	206	[redacted]	[redacted]	[redacted]	4.9 (4.7,	[redacted]	---	---

					5.5)			

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current).
§ One-sided p-value based on stratified log-rank test.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08NOV2017

Table 11. Summary of PFS Rate Over Time based on BICR per RECIST 1.1 (ITT Population IA1)

	Pembro Combo (N=410)	Control (N=206)	Total (N=616)
PFS rate at 3 Months in (95% CI)†	[redacted]	[redacted]	[redacted]
PFS rate at 6 Months in (95% CI)†	[redacted]	[redacted]	[redacted]
PFS rate at 9 Months in (95% CI)†	[redacted]	[redacted]	[redacted]
PFS rate at 12 Months in (95% CI)†	34.1 (28.8, 39.5)	17.3 (12.0, 23.5)	28.4 (24.4, 32.6)

† From the product-limit (Kaplan-Meier) method for censored data.
BICR = Blinded Independent Central Review
Database Cutoff Date: 08NOV2017

A3. The company notes on p 27 of the company submission that 'a change in hazard was observed again' to justify the use of a piecewise modelling approach for progression-free survival. Please clarify how the corresponding cut-off of Week 21 was chosen, and what is believed to underlie this change in hazard.

As per the NICE DSU TSD 14 document, since patient-level data are available from KEYNOTE-189, the cumulative and log-cumulative hazard plots were examined to allow the initial selection of appropriate models. Both plots demonstrate that the change in hazard was not constant over time ie. the plots are not straight lines. This change is more prominent in week 21 where the two arms are starting to separate.

Figure 8. Cumulative Hazard Plot – PFS (KN189 FA) – Week 21 Cut-point Marked in Blue

Figure 9. Log Cumulative Hazard Plot – PFS (KN189 FA) - Week 21 Cut-point Marked in Blue

The examination of Chow tests also shows a clear change in hazard in week 21 which is more prominent in the Chemotherapy arm:

Figure 10. KN189 FA – PFS Chow Test – Chemo

Figure 11. KN189 FA – PFS Chow Test – Pembro + Chemo

A4. The company notes on p 14 of the company submission that the analysis did not account for crossover of treatments 'since second-line treatment with immunotherapy is now SoC in the UK for patients regardless of PD-L1 expression levels'. Please clarify how this justifies the decision not to account for treatment switching.

The protocol for KEYNOTE-189 allowed subjects, with documented disease progression by RECIST 1.1, opportunity to crossover to receive pembrolizumab monotherapy if they were receiving saline placebo. [4] At the time of the submission at the point of CDF entry, only Pembrolizumab monotherapy (TA428) [5] was routinely used in UK clinical practice as a second line treatment for patients with PD-L1 TPS >1% this patient population. Therefore, cross-over adjustment was relevant for those patients who would not be eligible to receive Pembrolizumab monotherapy in the UK clinical setting; i.e. those patients whose tumours do not express PD-L1 (TPS<1%).

Subsequently, Atezolizumab monotherapy (TA520) was made available in the UK in May 2018 as a second line treatment option for patients irrespective of PD-L1 expression levels. Therefore, subsequent treatment switches from the control arm are likely to occur in UK clinical practice since a PD-L1/PD-1 inhibitor is available across all PD-L1 expression levels. Therefore, they form a relevant part of the analysis of overall survival, and it is not necessary to adjust for these treatment changes, in this current submission, since it is representative of realistic treatment patterns in the clinic.

A.2 Section B: Clarification on cost-effectiveness data

A.2.1 *Request for alignment of model with terms of engagement*

B1. Priority: Within the economic model provided by the company, it is not possible to replicate any results from the original submission (TA557) at the point of CDF entry (for Evidence Review Group [ERG] analyses, the Committee's preferred incremental cost-effectiveness ratios (ICERs) or the company's base case). This is because the "IA1" data have been removed from the company's updated model. Please can the company incorporate data from "IA1" within the version of the model sent as part of this re-appraisal.

The ERGs preference would be to have a model with functionality aligned with the terms of engagement. This outlines that the model would be expected to be capable of executing the following analyses:

- **Replication of the key cost-effectiveness results used in the committee's decision-making at the point of CDF entry**
- **Cost-effectiveness results that incorporate data collected during the CDF data collection period, with the assumptions used in the committee's decision-making at the point of CDF entry**
- **Cost-effectiveness results that incorporate data collected during the CDF data collection period plus any associated changes to the company's preferred assumptions**
- **Capacity to run the key sensitivity and scenario analyses presented in the original company submission.**

Without this, the ERG is unable to match scenarios across the two data sets and cannot confirm with absolute certainty that any further changes have not been undertaken within the cost-effectiveness model.

As discussed during the kick off meeting with NICE and ERG, MSD stated that, due to time restrictions, they were unable to provide one model with both IA1 and FA

data incorporated, and MSD understand that this was accepted. Therefore, MSD instead provided:

- a model named “MSD Submission CEM (ID1173) (ACIC) - IA1 - ERG assumptions” where the IA1 results can be replicated

- a model named “MSD Submission CEM (ID1584) (ACIC) - FA -ITT “ which is the same model as the above but two changes were made: 1) Data from IA1 were replaced with data from FA and 2) The background mortality was not implemented in the way the ERG preferred – justification is provided in p.39 of our CDF exit submission.

However, together with the clarification questions, MSD will provide a version of the FA model where the ERG will be able to replicate the IA1 results and the functionality to amend the settings in order to check whether any further changes were undertaken.

B2. Priority: Please can the company provide specific instructions on the settings which need to be selected so that the scenarios presented in the company submission in Section A.10 (Table 15 – Scenario 2a, 2b and 2c) can be replicated.

The specific changes made to the company’s preferred base-case analysis are not described in sufficient detail within the company submission to allow the ERG to produce these results.

Please note that Scenarios 2a, 2b and 2c are ***not*** the company’s preferred base-case analysis. As per the question in section A.10, Scenario 2 refers to the “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.” Therefore, in order to run the scenarios 2a, 2b, 2c, the settings in the FA model (named: MSD Submission CEM (ID1584) (ACIC) - FA -ITT” were selected to match exactly the ERG base case preferences in their IA1 model (named: “MSD Submission CEM (ID1173) (ACIC) - IA1 - ERG assumptions”):

- **SCENARIO 2a**

PFS: Weibull for both arms – 21 week cut off point
OS: Lognormal for both arms - week 0 cut off point
ToT: Exponential for Pembrolizumab combination arm, Weibull for chemotherapy arm

PAS:

[redacted]

[redacted]

Approach of Evaluating Utility: Utility by progression status

Is the long-term weekly hazard rate for mortality in Pembrolizumab + Chemotherapy patients equivalent to that for Chemotherapy patients?	Yes
If 'Yes', starting from what model year does the hazard rate become equivalent (value must be between 5 and 40 years)?	5

- **SCENARIO 2b**

PFS: Weibull for both arms – 21 week cut off point
OS: Gengamma for both arms - week 0 cut off point
ToT: Exponential for Pembrolizumab combination arm, Weibull for chemotherapy arm

PAS:

[redacted]

[redacted]

Approach of Evaluating Utility: Utility by progression status

Is the long-term weekly hazard rate for mortality in Pembrolizumab + Chemotherapy patients equivalent to that for Chemotherapy patients?	Yes
If 'Yes', starting from what model year does the hazard rate become equivalent (value must be between 5 and 40 years)?	5

- **SCENARIO 2c:**

PFS: Weibull for both arms – 21 week cut off point
OS: Loglogistic for both arms - week 0 cut off point
ToT: Exponential for Pembrolizumab combination arm, Weibull for chemotherapy arm

PAS:

[redacted]

[redacted]

Approach of Evaluating Utility: Utility by progression status

Is the long-term weekly hazard rate for mortality in Pembrolizumab + Chemotherapy patients equivalent to that for Chemotherapy patients?	Yes
If 'Yes', starting from what model year does the hazard rate become equivalent (value must be between 5 and 40 years)?	5

A.2.2 *Clarification on, and requests for, data and analysis outputs*

B3. Priority: Please can the company clarify what data are informing the Kaplan-Meier estimates presented in the company submission Figure 3 and Figure 4 for overall survival (OS) and Figure 6 and Figure 7 for progression-free survival (PFS).

The KM estimates presented in Figures 3, 4, 6 and 7 are from KEYNOTE-189 Final Analysis. These KM estimates can be found in the submitted cost-effectiveness model, in the tab named: “KN189 Main” columns C and G for PFS and OS respectively.

B4. Priority: Please can the company reproduce the figures created by placing the Kaplan-Meier data on top of the curves presented for the following Figures:

- Figure 3 (company submission, Section A.8.2, p.24)
- Figure 4 (company submission, Section A.8.2, p.25)
- Figure 5 (company submission, Section A.8.2, p.27)
- Figure 6 (company submission, Section A.8.3, p.28)
- Figure 7 (company submission, Section A.8.3, p.29)
- Figure 8 (company submission, Section A.8.3, p.31)
- Figure 9 (company submission, Section A.8.4, p.32)
- Figure 10 (company submission, Section A.8.4, p.33)
- Figure 11 (company submission, Section A.8.4, p.35)
- Figure 12 (company submission, Section A.8.4, p.36)

The ERGs preference would be for these to be reproduced with the following formatting:

- Kaplan-Meier curves placed on top of other modelled curves in black
- Clear legend outlining what each curve presents (e.g. modelled survival curve versus Kaplan-Meier curve)
- X-axis labelled in months or years (which may be more meaningfully/easily interpreted at the appraisal committee stage)

- Figure 3 (company submission, Section A.8.2, p.24)

Figure 12. Standard parametric fully fitted curves (starting week 0) for pembrolizumab combination arm – Overall Survival

- Figure 4 (company submission, Section A.8.2, p.25)

Figure 13. Standard parametric fully fitted curves (starting week 0) for pembrolizumab combination arm – Overall Survival

- Figure 5 (company submission, Section A.8.2, p.27)

Figure 14. Modelled OS fully fitted parametric curves vs KM curves for pembrolizumab combination and SoC arm

- Figure 6 (company submission, Section A.8.3, p.28)

Figure 15. PFS KM curve vs fitted piecewise model with cut-off at 21 weeks for pembrolizumab combination arm

- Figure 7 (company submission, Section A.8.3, p.29)

Figure 16. PFS KM curve vs fitted piecewise model with cut-off at 21 weeks for SoC arm

- Figure 8 (company submission, Section A.8.3, p.31)

Figure 17. Modelled PFS KM curves vs fitted piecewise model with cut-off at 21 weeks for pembrolizumab combination and SoC arm

- Figure 9 (company submission, Section A.8.4, p.32)

Figure 18. Standard parametric curves vs KM curve for ToT of pembrolizumab combination

- Figure 10 (company submission, Section A.8.4, p.33)

Figure 19. Standard parametric curves vs KM curve for ToT of SoC

- **Figure 11 (company submission, Section A.8.4, p.35)**

Figure 20. KM data and modelled ToT based on parametric curve fitting from pembrolizumab combination arm - exponential distribution

- Figure 12 (company submission, Section A.8.4, p.36)

Figure 21. KM data and modelled ToT based on parametric curve fitting from pembrolizumab combination arm - exponential distribution

B5. In the company economic model, it is stated that the dose intensity for pembrolizumab is 95.6% based on data from KEYNOTE-189 and 96.4% for chemotherapy. These values are the same as those reported in the original submission (TA557). Please can the company clarify if the dose intensities have changed with the later data cut?

The dose intensity for the pembrolizumab combination and for the control arm changed slightly to [redacted] and [redacted] respectively in the final analysis of KEYNOTE-189 (Table 12). The application of the updated dose intensity percentages in the economic model changes the base case ICER from [redacted].

Table 12. dose intensity of pembrolizumab combination and control arm

Dose Intensity
(ASaT Population)

	Pembro Combo	Control	Total
Subjects in population	405	202	607
Actual Number of Treatment Cycles			
Subjects with data	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Expected Number of Treatment Cycles			
Subjects with data	[redacted]	[redacted]	[redacted]

Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Percentage of Actual vs Expected Number of Treatment Cycles			
Subjects with data	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Expected number of treatment cycles by treatment duration. For subjects who crossed over to pembrolizumab from the control group, doses administered after crossover are excluded. (Database Cutoff Date: 20MAY2019)			

B6. Please can the company confirm that the AIC/BIC statistics presented in Table 12 (refer to company submission, p 30) are correct – notably for the exponential and Generalised Gamma parametric models, which may have been rounded to the nearest integer.

MSD can confirm that the data are correct as presented.

B7. Please can the company clarify (based on guidance provided in NICE DSU TSD 14) how the base-case curves for OS, PFS, and ToT were determined by the company. These curves are:

- **Log-logistic for OS for both SoC and pembrolizumab combination (company submission, Section A.8.2, p.23)**
- **Piecewise model – cut-off at 21 weeks followed by a Weibull curve (company submission, Section A.8.3, p.29)**
- **Exponential for ToT for both SoC and pembrolizumab combination (company submission, Section A.8.4, p.34)**

Please note that the information provided below was given originally in the CDF exit submission document in sections A.8.2, A.8.3 and A.8.4 as well as in the appendices document (due to word limit restriction in the submission document). For convenience, all three curve selections (OS, PFS and ToT) are again described in further detail below.

The guidance from the NICE DSU TSD14 was followed to identify base case parametric survival models for OS and PFS. In summary, the steps that were followed include:

1. Testing the proportional hazard (PH) assumption – To assess whether joint or separate statistical models were more appropriate for the pembrolizumab and SOC treatment arms:

   a. A statistical test of the PH assumption was performed

   b. The cumulative hazard plot, the log cumulative hazard plot and the Schoenfeld residual plot were visually assessed to determine if the data from KEYNOTE-189 indicated proportional effects between pembrolizumab and SOC.

2. Since there was evidence against the PH assumption, a pooled parametric model was deemed inappropriate. Therefore, independent, separate survival models were explored. All standard parametric models (i.e. exponential, Weibull, Gompertz, log-logistic, log-normal and generalized gamma) were separately fitted to each arm using data from the relevant treatment arm. Following the recommendation from the DSU, the same functional form was selected for the separate parametric models according to that fitting most closely the data overall.

3. 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) goodness-of-fit statistics were calculated to help identify the most plausible survival models.

4. Lastly, the choice of base case parametric models was validated in terms of clinical plausibility of both short-term and long-term extrapolations.

Overall Survival:

1. Testing the proportional hazard (PH) assumption

When the proportional hazard assumption was tested, there was not enough statistical evidence against “the proportion hazard ratio” assumption:

	Rho	chisq	p
TRT01PPembro Combo	0.0647	1.73	0.188

However, upon visual examination of the cumulative hazard plot and the log cumulative hazard plot it was evident that the proportional hazard assumption was violated since the two treatment groups crossed towards the beginning and the lines are not parallel. Also, the Schoenfeld residuals plot deviated from the y=0 horizontal line, which is an indication of a potential violation of the PH assumption.

Figure 22. Cumulative hazard plot for pembrolizumab combination and control arm

Figure *23*. Log cumulative hazard plot for pembrolizumab combination and control arm

Figure 24. Schoenfeld residual plot of OS for pembrolizumab combination and SoC based on KEYNOTE-189 (May 2019 data cut - FA)

Additionally, as seen at the OS log cumulative hazard plots, a change in the slope occurs around week 49 which indicates that a piecewise approach for the extrapolation might be appropriate. However, this was eventually tested only as a scenario analysis since - as will be discussed below- a loglogistic curve was selected as more appropriate for extrapolation. The choice of the loglogistic curve - as the ERG also noted on their report for the submission at the CDF entry point – indicates that it is not necessary to introduce cut-off points since the log-logistic curves are not constant over time.

2. All standard parametric models were separately fitted to the two arms

Figure 25. Standard parametric fully fitted curves (starting week 0) for pembrolizumab combination arm – Overall Survival

Figure 26. Standard parametric fully fitted curves (starting week 0) for SoC arm – Overall Survival

3. 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 13. Goodness-of-fit statistics (AIC/BIC) for pembrolizumab combination and SoC arm – Overall Survival

Pembrolizumab combination			SoC		
Fitted Function	ITT		Fitted Function	ITT	
	AIC	BIC		AIC	BIC
Exponential	3055.1	**3059.2**	Exponential	1757.1	1760.4
Weibull	**3053.4**	3061.4	Weibull	1759	1765.6
LogNormal	3073.9	3081.9	LogNormal	1747.3	1753.9
LogLogistic	3058.3	3066.3	LogLogistic	**1747.2**	**1753.8**
Gompertz	3054.5	3062.5	Gompertz	1757.1	1763.8
GenGamma	3055.4	3067.4	GenGamma	1749.1	1759.1

The loglogistic distribution provided the best statistical fit to the full OS KM data for the SoC arm and it's the fifth/fourth (AIC/BIC) better fit for the pembrolizumab combination arm. Whilst the exponential curve has the best statistical fit for the pembrolizumab combination arm, it was not deemed appropriate for selection as the proportional hazard assumption does not hold and the exponential distribution assumes proportional hazards. This is consistent with the ERG's and committee's conclusion in the ToE. Additionally, the cumulative hazard plot illustrates that the change in hazard is not constant over time as there are changes in the slope around week 49. This change further confirms that the exponential curve is not suitable as this curve assumes constant hazard.

4. Validation of the parametric extrapolation based on clinical plausibility

In terms of clinical plausibility, the exponential and the weibull distributions provided very low 5-year OS estimates (4%) for the SoC arm while the loglogistic provided a plausible estimate of 8.7% (according to ToE, 5-11% 5-year OS for the SoC is reasonable for decision making).

Finally, according to the ToE, the committee considered the loglogistic to be a potentially plausible curve and for consistency in addition to the above rationale, this curve was selected as the base case. As the second-best fitting curve for SoC and clinically plausible (5-year OS for SoC arm 9%) the lognormal was applied to both arms in a scenario analysis.

Progression Free Survival

1. Testing the proportional hazard (PH) assumption

The PH assumption was tested using the log cumulative hazards and the Schoenfeld residual test. Although based on the test result (p = 0.658) the PH assumption could

not be rejected, the visual inspection of the log cumulative hazard plot and the Schoenfeld residual plot did not support this assumption as the lines crossed. The Schoenfeld residuals plot deviated from the y=0 horizontal line, which is an indication of a potential violation of the PH assumption.

Figure 27. Cumulative hazard plot of PFS defined per RECIST v1.1 as assessed by BICR for pembrolizumab combination and SoC based on KEYNOTE-189 (May 2019 data cut - FA)

Figure 28. Log-cumulative hazard plot of PFS defined per RECIST v1.1 as assessed by BICR for pembrolizumab combination and SoC based on KEYNOTE-189 (May 2019 data cut - FA)

Figure 29. Schoenfeld residual plot of PFS defined per RECIST v1.1 as assessed by BICR for pembrolizumab combination and SoC based on KEYNOTE-189 (May 2019 data cut - FA)

Additionally, a change in the hazard was observed in week 21 and a piecewise apporoach seemed appropriate. Justification for the selection of this cutoff point is provided in question A3.

2. All standard parametric models were separately fitted to the two arms

All standard parametric curves were fitted to OS data after week 21 both for pembrolizumab combination and for the SoC arm separately.

Figure 30. PFS KM curve vs fitted piecewise model with cut-off at 21 weeks for pembrolizumab combination arm

Figure 31. PFS KM curve vs fitted piecewise model with cut-off at 21 weeks for SoC arm

3. 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 14. Goodness-of-fit statistics (AIC/BIC) for pembrolizumab combination and SoC arm – 21 weeks cut-off point– Progression Free Survival

Pembrolizumab combination			SoC		
Fitted Function	ITT		Fitted Function	ITT	
	AIC	BIC		AIC	BIC
Exponential	2387.9	2391.6	Exponential	856	858.6
Weibull	**2370.2**	**2377.6**	Weibull	847.5	**852.8**
LogNormal	2406.5	2413.9	LogNormal	873.5	878.8
LogLogistic	2385	2392.4	LogLogistic	866.5	871.8
Gompertz	2380.8	2388.2	Gompertz	856.2	861.5
GenGamma	2371.4	2382.5	GenGamma	**846**	854

Weibull distribution had the best fit for the pembrolizumab combination arm and for the SoC (with GenGamma having a marginally lower AIC statistic for the SoC arm) and upon visual inspection, Weibull was selected as the best fitting curve to extrapolate the PFS after week 21.

Time on Treatment

As per the KEYNOTE-189 protocol patients in both trial arms could discontinue at any time to due to adverse events, disease progression, inter-current illness, protocol non-compliance or investigator or patient preference. Additionally, in the case of disease progression, patients would continue on pembrolizumab post-progression if, in the investigator's treatment opinion, the patient was deriving benefit from treatment. Therefore, rather than assuming treatment terminated with disease progression, patient data corresponding to actual ToT were analysed to capture the actual utilisation and this is consistent with the submission at the CDF entry point

Separate parametric curves were fitted to the patient level treatment duration data from KEYNOTE-189 to represent ToT in the economic model.

Figure 32. Standard parametric curves for ToT of pembrolizumab combination

Figure 33. Standard parametric curves for ToT of SoC

The AIC/BIC statistics (Table 15) combined with visual inspection were used to select the ToT distribution for the base-case of the trial population, consistently with the submission at CDF entry point. The exponential and the GenGamma had the best statistical fit for both pembrolizumab combination and SoC. However, the exponential was used for the pembrolizumab combination arm in the submission at CDF entry point and for consistency, it was selected for both arms now.

Table 15. Goodness-of-fit statistics (AIC/BIC) for pembrolizumab combination and SoC arm - ToT

Pembrolizumab combination			SoC		
	ITT			ITT	
Fitted Function	AIC	BIC	Fitted Function	AIC	BIC
Exponential	3770.2	**3774.3**	Exponential	1737.1	**1740.4**
Weibull	3772.2	3780.2	Weibull	1736.5	1743.1
LogNormal	3904.2	3912.2	LogNormal	1812.8	1819.5
LogLogistic	3837.2	3845.2	LogLogistic	1782.7	1789.3
Gompertz	3769.7	3777.7	Gompertz	1739.1	1745.7
GenGamma	**3764.8**	3776.8	GenGamma	**1731.2**	1741.2

A.2.3 *Clarification on cost-effectiveness results*

B8. In Section A.14 (p.52) of the company submission, the company has stated that: "results from multiple sensitivity analyses showed the ICER to be consistently below [redacted] per QALY (discounted, with the patient access scheme [PAS])". Please can the company confirm that all key scenario analyses relevant for decision making are provided in Section A.12.

MSD can confirm that the all key scenario analyses were presented. MSD can also confirm that he statement was inaccurate as many of the scenario analyses presented were above £50,000 per QALY; however, it should be noted that none of the scenarios presented, provided a significantly higher ICER with the highest being under £55,000 per QALY.

B9. In Section A.12 of the company submission, Table 18 (p.49) presents key scenario analyses comparing pembrolizumab combination to SoC in a deterministic format. Please can the company also provide probabilistic results for these key scenario analyses?

The base-case deterministic ICER is [redacted] yet the probability of pembrolizumab combination being cost-effective based on the probabilistic analysis is 16.2% and the base-case probabilistic ICER is [redacted]. These [redacted] referenced by the company, and so the ERG considers it important that both deterministic and probabilistic results are available to inform the Committee's decision making.

Please find below the probabilistic results for all the scenario analyses presented in section A.12 of the company submission - Table 18.

Scenario analysis 1: Alternative parametric extrapolation: Fully fitted (week 0) lognormal

	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Trial chemotherapy arm	£42,884	1.15	-	-	-
Pembrolizumab + chemotherapy	£85,612	1.99	£42,728	0.84	£50,828

Scenario analysis 2: Piecewise extrapolation at week 49

	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Trial chemotherapy arm	£43,648	1.27	-	-	-
Pembrolizumab + chemotherapy	£86,062	2.06	£42,414	0.79	£53,749

Scenario analysis 3: 3-year cap on benefits of pembrolizumab combination from the start of treatment

	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Trial chemotherapy arm	£43,076	1.18	-	-	-
Pembrolizumab + chemotherapy	£85,286	1.94	£42,210	0.76	£55,211

Scenario analysis 4: 10-year cap on benefits of pembrolizumab from the start of treatment

	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Trial chemotherapy arm	£43,076	1.18	-	-	-
Pembrolizumab + chemotherapy	£86,150	2.07	£43,074	0.89	£48,433

Scenario analysis 5: Alternative combined method of estimating utilities

	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Trial chemotherapy arm	£43,076	1.13	-	-	-
Pembrolizumab + chemotherapy	£85,838	1.94	£42,762	0.80	£53,230

A.3 Section C: Textual clarification and additional points

C1. company submission – p 27 Section A.8.3 'A range of standard parametric curves were fitted to OS data after Week 21' – from the ERG's understanding this should say 'PFS'. Please could the company clarify.

MSD can confirm that the sentence should read: "A range of standard parametric curves were fitted to *PFS* data after Week 21"

C2. company submission – p 30 Section A.8.3 'The modelled PFS curves based on the approach described above are presented in and Error! Reference source not found.**.' – the ERG believe this should say 'PFS and OS'. Please could the company clarify.**

The sentence should read: "The modelled PFS curves based on the approach described above are presented in **Error! Reference source not found.**."

OS curves (and Figure 5) have been described in section A.8.2

REFERENCES

1. National Institute for Health and Care Excellence. Terms of Engagement for CDF review - Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer (TA557). 2019.
2. National Institute for Health and Care Excellence. Cancer Drugs Fund – Data Collection Arrangement - Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-squamous non-small-cell lung cancer [ID1173]. 2018
3. Merck Sharp Dohme. Keytruda (MK-3475) HTA Report. Indication: First-line Metastatic Non-Squamous NSCLC. Indirect Treatment Comparison. Pembrolizumab in Combination with Chemotherapy versus Pembrolizumab Monotherapy. Scenario 1: Proportional Hazards. Table 9. Indirect Treatment Comparison Overall Survival - Studies 189+021G and 042+024 Population adjusted Analysis (Intention-to-Treat Population, TPS ≥ 50%). October 03, 2019. Merck data on file.
. 2019.
4. Merck Sharp D. KN189 Protocol: A Phase I/II Study of MK-3475 (SCH900475) in Combination with Chemotherapy or Immunotherapy in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma. 2016.
5. National Institute for Health and Care Excellence. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. Technology appraisal guidance [TA428]. . 2017.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (CDF Review of TA557) [ID1584]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research and work in lung cancer patient care (information, support and advocacy activity) and raising awareness of the disease and issues surrounding it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of solid tumours, such as lung cancer
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of over 55 monthly Lung Cancer Patient Support Groups, patient/carer panel, online forums and its Lung Cancer Information Helpline

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	According to the National Lung Cancer Audit, the one year survival for lung cancer is 37%. Thus, this group of lung cancer patients, with advanced/metastatic disease have a particularly poor outlook, with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	As above, despite current therapy, outcomes for those with advanced/metastatic disease remains poor. In recent years, immunotherapy has brought a new therapy option.
8. Is there an unmet need for patients with this condition?	Yes
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The potential for extensions in life, is of paramount importance to this patient population and their families. This therapy, being available through the CDF has ensured patient access in this indication.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The recorded side effects of this therapy.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Immunotherapy is an important therapy option for patients with non small cell lung cancer
- Having been available in this indication through the CDF, we hope that the necessary data is now available for the Appraisal committee to make a positive recommendation
-
-
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (CDF Review of TA557) [ID1584]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Samreen Ahmed**
2. Name of organisation	**BTOG/ACP/RCP/NCRI**

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? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Palliative chemotherapy/immunotherapy combination for NSCLC to improve QOL and extend survival
8. 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.)	Clinical improvement should be supported by radiological evidence of response. RECIST criteria for trials adopted
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	SOC would be platinum/pemetrexed doublet. There is a real desire to improve survival beyond 12 months
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Chemotherapy with cisplatin/carboplatin and pemetrexed has been superseded by carb/pemetrexed/pembrolizumab since its approval >12 months ago
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE ESMO/ASCO
• 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.)	1st line treatment, pathway of care is clearly defined. UK experience
• What impact would the technology have on the current pathway of care?	Has been reasonably easy to incorporate into 1st line treatment of lung cancer
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Longer time in the chemotherapy suite chair. Toxicity is largely the same as that with chemotherapy alone

• How does healthcare resource use differ between the technology and current care?	Longer time spent having treatment
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Already introduced into pathway of treatment without difficulty
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Keynote 189 Final analysis: At data cutoff (May 20, 2019), median (range) time from randomization was 31.0 (26.5–38.8) mo. Median OS: 22.0 vs 10.6 mo; HR 0.56 [95% CI, 0.46–0.69]) PFS: 9.0 vs 4.9 mo; HR 0.49 [95% CI, 0.41–0.59]) The 2-y OS rate was 45.7% vs 27.3% All favouring carbo/pemmetrexed/pembrolizumab vs chemotherapy alone
• Do you expect the technology to increase length of life more than current care?	There is more than doubling of OS Landmark survival of 2 years is 45%

• Do you expect the technology to increase health-related quality of life more than current care?	As there is better control of lung cancer, QOL is likely to improve. Toxicityis manageable in the maintenance part fo the schedule Pemetrexed and pembrolizumab continue until progression or toxicity. Max of 2 years
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	All groups benefit **HR (95% CI)** / **All pts N = 616** / **PD-L1 TPS ≥50% n = 202** / **PD-L1 TPS 1-49% n = 186** / **PD-L1 TPS < 1% n = 190** OS: 0.56 (0.46–0.69) / 0.59 (0.40–0.86) / 0.66 (0.46–0.96) / 0.51 (0.36–0.71) PFS: 0.49 (0.41–0.59) / 0.35 (0.25–0.49) / 0.53 (0.38–0.74) / 0.67 (0.49–0.93) PFS2: 0.50 (0.41–0.61) / 0.52 (0.36–0.75) / 0.57 (0.40–0.81) / 0.47 (0.33–0.66)
The use of the technology	
14. 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	Longer time on chemotherapy suite as 3 drugs

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	2 years max Toxicity or clinical / radiological progression
16. 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?	None
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	With longer survival with 1st line treatment, there are fewer patients lost with attrition from 1st to 2nd line due to deterioration in PS and decline in QOL

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes overall survival in all groups is twice as better that SOC
• Does the use of the technology address any particular unmet need of the patient population?	None
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Manageable in real life aswell compared to chemotherapy alone
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK	YES SOC comparator is UK standard

clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes PFS OS PFS2
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	2 yr landmark analysis
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None
20. Are you aware of any relevant evidence that might	

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA557?	Nivolumab/ipilumimab checkmate 227 Carbo/taxol/atezo/bevacizumab Impower 150
22. How do data on real-world experience compare with the trial data?	Very comparative to trial data Many real life reviews conducted as new regime introduced
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
23b. Consider whether these issues are different from issues with current care and	

why.None	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Doubling of overall survival
- No additional toxicity compared to chemotherapy alone
- Will lose less patients between 1st and 2nd line treatment
- Increase 1st line time on chemotherapy chairs
- Real life experience similar to study findings

Thank you for your time.

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

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Clinical expert statement

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (CDF Review of TA557) [ID1584]

Thank you for agreeing to give us 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.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Yvonne Summers**
2. Name of organisation	**The Christie NHS Foundation Trust**

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 this condition? **X**☐ a specialist in the clinical evidence base for this condition 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.) **Have not seen the submissions**
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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To induce response, help symptoms, improve survival and prevent progression
8. 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.)	Improvement in OS of 3 months or more is clinically relevant. A doubling of OS as seen in KEYNOTE 189 is impressive (10.7 to 22 months)
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Despite improvements in care in recent years, outcomes remain very poor for patients with NSCLC without a molecular driver (EGFR, ALK, ROS1, RET). The majority of patients without a driver still experience progression of their cancer and death within 2 years of diagnosis of advanced disease.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	According to standard NHS commissioning patients are treated with platinum doublet chemotherapy (usually platinum pemetrexed) if PD-L1<50%. Patients with PD-L1 50%+ can be treated with single agent pembrolizumab. Since the CDF access to Pem Pem Platinum was given, patients of PS0-1 with no contraindications to immunotherapy have been treated with this combination. For patient with PD-L1 50%+ most are still treated with pembrolizumab alone and others (depending on clinical characteristics such as critical central disease) are treated with the combination.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The combination treatment is recommended in ESMO (PS 0-1), ASCO (PS 0-1) and NCCN guidance. ESMO guidance is usually adhered in the UK providing there is access to the treatment in the UK
• 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.)	The pathway has some room for individual clinician/patient choice, particularly since the COVID 19 pandemic has allowed a greater range of therapies: there are number of considerations which influence treatment choice: • performance status • comorbidities and frailty • burden of disease • Site of disease (eg impinging on airways where progression of cancer may have irreversible consequences) • Patient choice (eg some may want to avoid chemotherapy) • Local capacity and ability to deliver treatment (immunotherapy can be given 6 weekly compared to 3 weekly for chemotherapy, but continues for a longer duration) • Potentially more concern about chemotherapy, myelosuppression and risk of COVID mortality
• What impact would the technology have on the current pathway of care?	Compared to standard NHS commissioning (ie chemotherapy without immunotherapy) there are more visits as the majority of patients had 4 cycles of chemotherapy and only a minority received maintenance pemetrexed.

	Patients on the triplet continue treatment until disease progression. This pathway has of course been operational since the triplet has been available via the CDF. The extent to which the triplet therapy has been brought into clinical practice varies across the country and has been affected (stopped/slowed) by the COVID 19 pandemic. Centres where the clinical trials were running were more likely to adopt this as SoC than those with less familiarity with combination treatments. Second line treatments are affected in that as immunotherapy has moved up to 1st line, second line treatment becomes docetaxel +/- nintedanib (as it was prior to immunotherapy treatments being developed). When immunotherapy is used up front it will not be used again unless it is as part of a clinical trial.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The use of the technology, which has occurred whilst the triplet has been available via the CDF would continue. There have been some changes to treatment during COVID which may need to be considered eg single agent immunotherapy has been allowed as 1st line therapy for patients with PD-L1<50%.
• How does healthcare resource use differ between the technology and current care?	No change compared to current (CDF adherent) practice. Significant change compared to previous standard commissioning: • Treatment continues until PD or 2 years (most chemotherapy alone patients stop after 3 months, but same treatment schedule for single agent pembrolizumab) therefore increased resource use in terms of treatment administration and outpatient review. Radiology costs similar. • Potentially higher toxicity with triplet (increased outpatient/inpatient attendance costs) • Cost of managing immunotherapy toxicity (eg. rarely infliximab is used)
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care (oncology outpatients)

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Immunotherapy is already embedded in clinical practice in melanoma, lung cancer and increasingly in other cancers. Investment in treatment capacity to deliver ever increasing indications and duration of therapy is required. Delivery of the treatment out of hospital (in the patients home or closer to home at a mobile or satellite unit) may need to be considered. Specialist immunotherapy toxicity management services are developing across the country (eg Clatterbridge)
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Compared to standard chemotherapy, yes. Improvements in PFS and OS We are already seeing many more longer term survivors in clinics than previously. There is a tail to the survival curve seen in clinical practice. I now routinely have several patients in clinic who are 3/4/5 years since diagnosis, who have been treated with immunotherapy, which was previously an uncommon event.
• Do you expect the technology to increase length of life more than current care?	Yes, see comments above. Data from KEYNOTE 189 will be explored in detail during the review, however a key point is that longer follow up (23.1 months) of KEYNOTE 189 showed a doubling of OS [22.0 (CI 19.5- 25.2) vs 10.7 (CI 8.7-13.6) months (HR 0.56; CI 0.45-0.70)] and substantial increase in 2 year survival (45.5% vs 29.9%) with no increase G3-5 adverse events. The survival benefit was seen across the PD-L1 subgroups and there was no crossover of the initial part of the KM curve (unlike single agent immunotherapy trials eg KEYNOTE 042).
• Do you expect the technology to increase health-related quality of life more than current care?	Yes due to improvements in OS and PFS and good QoL when chemotherapy doublet stops. This observation is bourne out by the QoL outcomes reported for the study using EORTC QLC-C30 and QLQ- LC13 (JCO, Garrasino et al 2018)

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are a number of populations who were excluded or there was limited data from the original trials where further trial data, real life data, clinical experience is being accrued: • Performance status 2 • Pre-existing auto immune conditions • Treated and asymptomatic brain metastases
The use of the technology	
14. 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.)	The technology is already adopted as SoC for PS0-1 patients with no other contraindications in most centres. Many patients do not meet the criteria for treatment due to poor PS. There has, however, been less use of the triplet during the COVID 19 pandemic due to the wish of clinicians and patients to avoid myelosuppression from chemotherapy. More single agent pembrolizumab is likely to have been used since March 2020 for this reason, particularly in the PD-L1>50% group. I would expect the use of triplet therapy to increase when the COVID 19 risk declines further and when clinicians become more experienced with managing patients on this regimen. The triplet requires: • More chemotherapy suite chair time • The treatment has to be 3 weekly for the first 3 months (whereas pembrolizumab can be 6 weekly,

	although many centres initially treat 3 weekly until the 1st scan) • Increased risk of AE's including immune related AE's • More routine blood tests (TFT's and Cortisol)
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will stop on clinically relevant PD, significant toxicity or 2 years of therapy. No additional testing, but as survival times are improved there will be more scans, clinic visits, blood tests (including regular TFT's and cortisol) and need for CNS support than for patients on standard chemotherapy because patients are alive for twice as long.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	no
17. Do you consider the	Yes, we may even see a very small number of "cured" patients, particularly in the group who have had to

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?	stop treatment due to side effects.
• Is the technology a 'step-change' in the management of the condition?	It is a logical next step in the therapy of NSCLC patients (moving from 2nd line to 1st line),but is a step change in the improvement in outcomes
• Does the use of the technology address any particular unmet need of the patient population?	Yes improvement in survival, which remains dismal (<1year) with chemotherapy alone.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Despite increased AE's on triplet therapy the QoL is improved particularly later on in treatment when the platinum has stopped. Most of the toxicity in the 1st 3 months is chemotherapy related.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	OS, PFS, QoL, (RR)
• 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?	There has been a move to 6 weekly pembrolizumab therapy during COVID. There has been some discussion in the clinical community about whether the 6 weekly regimen has led to increased toxicity. Audit of data is required
20. Are you aware of any	SACT database/CDF data will be helpful

relevant evidence that might not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA557?	Single Agent pembrolizumab has been available during the COVID 19 pandemic for patients with PD-L1 <50% to reduce toxicity, although use has not been widespread as there has been some concern about whether this is best choice for patients given the inferior trial outcomes. This was not originally considered as a comparator for the whole population, only the PD-L1>50% subgroup.
22. How do data on real-world experience compare with the trial data?	I suspect that treatment discontinuation rates for the triplet may be a little higher than in the trial as real world patients have more co-morbidities. We have and on-going audit, but data are immature. Where real life data on outcomes of advanced NSCLC patients treated with immunotherapy have been reported they generally report similar OS and toxicity.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	no

23b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Treatment with platinum, pemetrexed and pembrolizumab substantially improves overall survival by for patients with advanced NSCLC compared to chemotherapy alone [22.0 (CI 19.5- 25.2) vs 10.7 (CI 8.7-13.6) months (HR 0.56; CI 0.45-0.70)]
- There a substantial increase in 2 year survival (45.5% vs 29.9%) with a tail to the survival curve which is apparent in clinical practice
- The treatment improves QoL compared to chemotherapy, particularly after the platinum component stops
- The crossing of the survival curves seen initially with immunotherapy alone versus chemotherapy is not evident with the triplet combination ie there are not avoidable early deaths due progression on immunotherapy
- The triplet treatment is recommended for the 1st line treatment of PS0-1 patients with advanced non-squamous NSCLC is ESMO, ASCO and NCCN guidelines

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Paula Shepherd**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? **X.** other (please specify): Lung cancer specialist nurse
3. Name of your nominating organisation	LCNUK (lung cancer nursing uk)
4. Did your nominating organisation submit a submission?	☐ yes, they did **X** no, they didn't ☐ I don't know
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. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: X I am drawing on others' experiences. Please specify how this information was gathered: I have been involved in the care of lung cancer patients since 2001 and became a lung cancer specialist nurse in 2011. During consultations with patients and their carers they have discussed their experiences surrounding lung cancer and treatments. I also facilitate a lung cancer patient support group.
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	During the diagnostic phase, patients often struggle with the uncertainty of what treatment they may/may not be offered and their prognosis. There is often a concern regarding potential side effects balanced with quality of life. Patients and carers often require support with decision making.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Some patients base their knowledge of lung cancer treatments on a relative or friends experience in the past. They are often surprised that there are different treatment options available now. I have received positive and negative feedback from patients surrounding lung cancer treatments, however these are based around their own personal experiences.
10. Is there an unmet need for patients with this condition?	Unfortunately lung cancer is still quite a taboo subject and patients still experience a blame culture at times. Late diagnosis of lung cancer remains an issue, however there have been some advances over the last few years.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The advantages expressed by patients are that they feel that they have more options available and improved response rates.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The side effects of treatment and with toxicities it can be difficult for health care professionals to differentiate which drug has caused the effects. This can lead to hospital admissions.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All patients should be reviewed for treatment based on a number of factors that are individual to them.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Unable to answer**
Other issues	
15. Are there any other issues that you would like the committee to consider?	N/A

Key messages
16. In up to 5 bullet points, please summarise the key messages of your statement: • • • • •

Thank you for your time.

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

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Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small cell lung cancer [ID1584]

Cancer Drugs Fund Review of TA557

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
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Author Contributions:	
Louise Crathorne	Conducted, reviewed and critiqued the clinical-effectiveness evidence. Coordinated the project and the report.
Simone Critchlow	Conducted, reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses
Jess Mann	Conducted, reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses
Ash Bullement	Conducted, reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses
G.J. Melendez-Torres	Conducted, reviewed and critiqued the network meta-analysis. Reviewed and provided comments on the report. Guarantor of the report.

Table of Contents

List of tables

List of Figures

Abbreviations

AE	adverse event
AIC	Akaike information criterion
ALK	anaplastic lymphoma kinase
ASaT	All subjects as treated
AUC	area under the curve
BIC	Bayesian information criterion
CDF	Cancer Drugs Fund
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CS1	company submission (TA557)
CS2	company submission CDF Review
CT	chemotherapy
DoR	duration of response
DSU	Decision Support Unit
EGFR	epidermal growth factor receptor
EQ-5D	EuroQol five dimension
ERG	Evidence Review Group
FA	Final analysis
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
IA	interim analysis
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meier
mths	months
N/A	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
NSCLC	non-small-cell lung cancer

ORR	objective response rate
OS	overall survival
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PD-L1	programmed death-ligand 1
PFS	progression free survival
PSA	probabilistic sensitivity analysis
Q3W	every three weeks
QA	quality assessment
QALY	quality adjusted life year
RCT	randomized controlled trial
SD	standard deviation
SLR	systematic literature review
SoC	Standard of care
TA	Technology Appraisal
ToE	Terms of engagement
ToT	time on treatment
TPS	tumour proportion score
TSD	Technical Support Document
TTD	Time to death
TWE	treatment waning effect
vs	versus
WTP	willingness to pay

1. EXECUTIVE SUMMARY

1.1. Critique of the adherence to committees preferred assumptions from the Terms of Engagement in the company's submission

The company has adhered to the majority of the committee's preferred assumptions from the Terms of Engagement (ToE); the key deviations are:

- Comparison with "other chemotherapy" (chemotherapy (that is, docetaxel, gemcitabine, paclitaxel or vinorelbine as monotherapy), with carboplatin or cisplatin, with or without pemetrexed maintenance therapy. Results for this comparison were not presented in CS2 although the company discussed its rationale during the kick-off meeting and in the report for CS2.

- Overall survival (OS) extrapolation: The committee noted that the log-logistic and generalised gamma curves were potentially plausible curves for extrapolation. The company explored log-logistic extrapolation but did not explore generalised gamma curves to model OS.

- Approach to utilities: The company deviated from the committee's preference to calculate utilities using progression status with a quality-of-life decrement associated with time to death of less than 360 days Instead the company applied utilities based on time-to-death and applied a decrement applied in the progression health-state.

Other assumptions explored by the ERG to assess the impact on the ICER are noted in Section 1.3.

1.2. Summary of the key issues in the clinical effectiveness evidence

Pembrolizumab plus standard chemotherapy (pemetrexed and platinum-based chemotherapy) (referred to as pembrolizumab combination therapy) was compared to placebo in adults with untreated, metastatic, non-squamous NSCLC whose tumours have no EGFR or ALK positive mutation. Evidence was taken from the final analysis of the KEYNOTE-189 trial.

The final analysis reinforced the interim analysis (IA1) data reported in TA557 (CS1), indicating that pembrolizumab combination therapy is likely to offer a survival benefit (both progression free survival [PFS] and overall survival [OS]) in comparison to placebo combination therapy (reflective of standard of care, chemotherapy).

The original scope (TA557), had included other chemotherapy treatments as a comparator in the wider population (docetaxel, gemcitabine, paclitaxel or vinorelbine as monotherapy with carboplatin or cisplatin, with or without pemetrexed therapy). In CS1 the company had presented a network meta-analysis (NMA) comparing pembrolizumab combination therapy with "other chemotherapy" which indicated no significant difference between the platinum doublet chemotherapy interventions commonly used in UK clinical practice. While the ERG accepted the rationale provided, it also noted that the degree to which new evidence would have changed the conclusions of the NMA is unclear. The ERG also acknowledged the clinical feedback given at the time of TA557, that platinum + docetaxel, platinum + paclitaxel, and platinum + paclitaxel + bevacizumab were not commonly used in UK clinical practice. The company also noted that the CDF Clinical Lead had commented that pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was the relevant comparator which is confirmed in the documentation referenced by the company in CS2.

Pembrolizumab combination therapy was compared with pembrolizumab monotherapy in a subgroup of patients who were PD-L1+ tumour proportion score (TPS) ≥50%. The company provided results for this subgroup in CS1 and while not reported in CS2 the company provided results during clarification. The company presented an ITC for which the methods were considered broadly appropriate. Results suggested a numerical improvement in OS and a potential benefit in PFS; however, the latter should be interpreted with caution as tests for proportional hazards assumptions were not presented and visual inspection of curves suggested these assumptions were untenable.

No further subgroups were presented by the company in the submission. However, the ERG regarded that the relevant subgroup which impacted the decision problem had been recognised and included in the company's FA model.

1.3. Summary of the key issues in the cost effectiveness evidence

The ERG considered five key issues which impact the cost-effectiveness evidence:

- **Overall survival extrapolation (Section 4.1.5 and Section 4.1.5.1)**

  Although log-logistic curves were considered to be plausible long-term extrapolations of the OS data (Decision Support Unit [DSU] Technical Support Document [TSD] 14), in TA557 the committee agreed that the generalised gamma may also be an appropriate fit. Based on the updated data from the final analysis (FA), both the generalised gamma and the log-

logistic were considered as plausible extrapolations. The company did not include generalised gamma curves in the base case or as a scenario in CS2. The ERG has therefore provided this as a scenario and also explored the impact of using the generalised gamma for the pembrolizumab arm and a log-logistic for the SoC arm.

- **Treatment waning effect (TWE) (Section 6.1.3)**

  A treatment waning effect was applied to the pembrolizumab combination arm of the economic model. During TA557, both three years and five years were recognised as relevant points at which the treatment effect may start to taper. However, the ERG understand that a waning effect can be more gradual over time. Given treatment waning is an area of uncertainty which impacts the ICER, the ERG considered a scenario where treatment waning is applied from the point of stopping pembrolizumab (Year 2) and occurs gradually until Year 5. This approach assumed a linear transition from the hazards of the pembrolizumab combination curve to the hazards of the SoC curve (over the three years).

- **Time on treatment (ToT) (Section 4.1.5.3)**

  The company used an exponential curve for both the pembrolizumab combination and SoC arm. In doing this, the company assumed proportional hazards between the two arms for this outcome. However, no evidence was provided by the company to support this approach. While the ERG considered the exponential models to be a reasonable fit to the Kaplan-Meier curves for both treatment arms, it believed that the model underestimated the KM curve between Years 1 and 2 and it was unclear why the rate of discontinuation could be assumed constant, when considering a combination treatment consisting of three components, one of which is assumed to be withdrawn at exactly two years. Following guidance from the DSU TSD 14, the ERG considered the generalised gamma more appropriate based on the AIC/BIC statistics.

- **Application of utilities (Section 4.1.6)**

  The ERG noted that the base case in CS2 incorporated utilities based on time to death (TTD) with an additional decrement applied for progression. This approach was different to that used in CS1, which the company noted was in response to clinical opinion and committee preference in TA557. In TA557, two methods had been discussed which incorporated both progression and time-to-death within the estimation of utilities: progression-based utilities with a decrement applied in the last year of life (Approach 1) and

TTD utilities with a decrement applied to account for progression (Approach 2). The ERG noted, however, that the company incorporated Approach 2 while the Committee preference in TA557 was Approach 1. The ERG noted that the utility decrement from either method had not been varied in one-way sensitivity analysis (OWSA) or probabilistic sensitivity analysis (PSA). The ERG's preferred approach was the application of utilities based on progression with a TTD decrement to people with <360 days to live.

- **Dose intensity**

  Although there was little difference from the dose intensity in the IA, the ERG considered it more appropriate to include the updated dose intensity from the FA.

1.4. Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions based on the new data presented are as follows:

- Generalised gamma distributions assigned to both treatment arms for OS.
- Application of a gradual TWE between Year 2 and Year 5.
- Generalised gamma distribution assigned to both arms for ToT.
- Updated dose intensity from KEYNOTE-189 FA.
- Utility Approach 1 explored (application of utilities based on progression with a time to death [TTD] decrement applied to people with <360 days to live).

Implementation of the ERG's preferred assumptions surrounding these parameters increases the company's submitted incremental cost-effectiveness ratio (ICER) by [redacted] [redacted].

Table 1: ICER resulting from ERG's preferred assumptions (deterministic base case)

	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER £/QALY
Chemotherapy	[redacted]	[redacted]			
Pembro + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; Pembro, pembrolizumab; QALYs, quality adjusted life years

1.5. Summary of exploratory and sensitivity analyses undertaken by the ERG

Exploratory and sensitivity analyses undertaken by the ERG are presented in Table 2

Table 2: Exploratory analyses undertaken by the ERG

Scenario analyses conducted by the ERG	Section in main ERG report	Pembro + chemotherapy		Chemotherapy		ICER £/QALY
		QALYs	Costs	QALYs	Costs	
Company base-case	Sn 5.1.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon						
1. 25-year time horizon	Sn 4.1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival						
2. Generalised gamma applied to both treatment arms	Sn 4.1.5.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Generalised gamma applied to the pembrolizumab arm	Sn 4.1.5.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gradual treatment waning affect						
4. Gradual TWE applied between years 2 to 5	Sn 6.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Gradual TWE applied between years 2 to 3	Sn 6.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. Gradual TWE applied between years 3 to 5	Sn 6.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Gradual TWE applied between years 3 to 10	Sn 6.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time-on-treatment						
8. Generalised gamma parametric distribution for time-on-treatment applied to both treatment arms	Sn 4.1.5.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose intensity						
9. Updated dose intensity from the final analysis of KEYNOTE-189	Sn 4.1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; Pembro, pembrolizumab; QALYs, quality adjusted life years; TWE, treatment waning effect

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

2.2. Background

Pembrolizumab with pemetrexed and platinum chemotherapy is recommended for use within the Cancer Drugs Fund (CDF) as an option for untreated metastatic non-small-cell lung cancer (NSCLC) in adults whose tumours have no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)-positive mutations. It is recommended only if pembrolizumab is stopped at two years of uninterrupted treatment, or earlier if disease progresses, and the conditions in the managed access agreement are followed.

The key clinical evidence was taken from the Phase 3 trial KEYNOTE-189.[1-3] At the most recent data cut (November 2017) during the appraisal at the CDF entry point, median overall survival (OS) for pembrolizumab combination was not reached.[2;3] The median follow-up was 10.5 months (0.2 to 20.4 months).[2] The committee considered that the survival evidence was too uncertain given the immaturity of the data presented.[4;5] The immaturity of the trial data led to uncertainty in the extrapolation of the survival data over the time horizon of the economic model.[4;5]

2.3. Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

The key committee preferred assumptions from the terms of engagement (ToE)[6] are summarised in Table 3.

Table 3: Summary of committee preferred assumptions from TA557

Area	Committee preferred Assumptions in TA557	Addressed in the company submission (CS)	Rationale if different from the terms of engagement	ERG comment
Population	Adults with untreated, metastatic, non-squamous NSCLC lacking EGFR- and/or ALK-positive mutation	Adults with untreated, metastatic, non-squamous, NSCLC lacking EGFR and/or ALK mutation	N/A	The company presented data from the FA for the ITT population from the KEYNOTE-189 trial which included adults with untreated, metastatic, non-squamous, NSCLC lacking EGFR and/or ALK mutation
Comparative evidence	NMA to compare pembrolizumab combination with other chemotherapy treatments used in NHS practice: committee were satisfied with methods	No	Results from the NMA conducted in CS1 showed no statistically significant difference between the specified platinum doublet chemotherapy interventions. The company referenced expert clinical advice given in TA557 that platinum doublet chemotherapy interventions were not commonly used in UK clinical practice. The company further argued that in the appraisal of atezolizumab (TA520), pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was considered the relevant comparator for the for first-line non-squamous NSCLC population by the CDF clinical lead.[7]	The ERG was broadly satisfied with the methods of the NMA that was presented in CS1. While the ERG accepted the rationale provided, it also noted that the degree to which new evidence would have changed the conclusions of the NMA is unclear. The ERG acknowledged the clinical feedback given at the time of TA557 that platinum + docetaxel, platinum + paclitaxel, and platinum + paclitaxel + bevacizumab were not commonly used in UK clinical practice.
	ITC to compare pembrolizumab combination with pembrolizumab monotherapy for people whose tumours express PD-L1 with ≥50% TPS: effect large and 95% credible	ITC of pembrolizumab combination vs pembrolizumab monotherapy was updated and results presented for the PD-L1+ TPS ≥50% in clarification	N/A	The ITC of pembrolizumab combination vs pembrolizumab monotherapy was updated and results presented for the PD-L1+ TPS ≥50% was presented during clarification. At variance

Area	Committee preferred Assumptions in TA557	Addressed in the company submission (CS)	Rationale if different from the terms of engagement	ERG comment
	intervals around the effect very wide and the difference not statistically significant; company did not include data from a relevant trial KEYNOTE-021G (although committee agreed it would not have a substantial effect on the final estimate; further data from KEYNOTE-189 could help to reduce the uncertainty in the OS estimates			with the analysis presented in TA557, four trials (KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, KEYNOTE-021G) were used, thus integrating all available trial evidence. The methods were considered broadly appropriate.
Economic analysis				
Model structure	The company's model structure is appropriate for decision making.	N/A	N/A	N/A
Stopping rule	Two-year stopping rule is appropriate given current available evidence but should be reviewed in light of new evidence	N/A	N/A	N/A
OS and OS extrapolation	Committee considered there were potentially plausible curves which provided clinically plausible 5-year OS for the SoC arm, including the log-logistic and generalized gamma curves.	Log-logistic model	N/A	The ERG noted that the company did not explore generalised gamma curves to model OS. The ERG also considered the generalised gamma curve

Area	Committee preferred Assumptions in TA557	Addressed in the company submission (CS)	Rationale if different from the terms of engagement	ERG comment
Background Mortality	An adjustment for background mortality should be included	Background mortality was not implemented, however the modelled OS has been capped by the survival rate for the general population	The company believed that the OS data of the KEYNOTE-189 trial captured all-cause mortality, therefore meaning that the fully fitted extrapolated curve takes into account dying from other causes, and the implementation of background mortality could, therefore, be considered as double-counting.	The ERG agreed with the company's approach.
PFS	The Committee stated no preference – it is assumed that the company's original model for PFS (KM with 21-week cut-off, then Weibull distribution) is suitable	KM with 21-week cut-off then Weibull distribution	N/A	N/A
ToT	The committee stated no preference – it is assumed that the company's original model for ToT (exponential for pembrolizumab combination therapy, and Weibull for SoC) is suitable	Exponential for both arms	The company found that both the exponential and the generalised gamma had the best statistical fit for both treatment arms (using AIC/BIC statistics and visual inspection). For consistency with the submission at the CDF entry point, the company therefore decided upon use of the exponential for the extrapolation of ToT for both arms.	The ERG considered it was inappropriate to assume constant hazards for ToT and instead selected a generalised gamma curve to inform the ERG base case.
Approach to Utilities	Preference to calculate utilities using progression status with a quality-of-life decrement associated with time to death of less than 360 days applied for patients who are likely to live less than 360 days	TTD was used, with a quality-of-life decrement associated with PD applied for patients who had progressed	N/A	The ERG has selected to apply the committee preferred assumption from TA557. A progression based approach applying a decrement for patients who are likely to live less than 360 days.

Area	Committee preferred Assumptions in TA557	Addressed in the company submission (CS)	Rationale if different from the terms of engagement	ERG comment
Treatment effect	Preference to cap the benefit of pembrolizumab at 3 years and 5 years from the start of treatment	A 5-year cap from the start of treatment was implemented on the treatment duration, as a base case. A 3-year and 10-year cap, as well as a lifetime treatment effect, is presented as scenario analysis.	The company believed that there was no evidence to suggest that the treatment effect stops after a certain time point.	The ERG has implemented a gradual treatment waning approach applied between two years and five years.
End of life	Pembrolizumab combination compared with chemotherapy (both plus carboplatin or cisplatin) met NICE's end-of-life criteria Pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% tumour proportion score did not meet NICE's end-of-life criteria	N/A	N/A	While the company results indicated that, the undiscounted life years were 2.00 for the SoC arm; survival was predicted to be exactly 24 months – the cut-off for the end-of-life criteria. Despite this, the other five extrapolated curves indicated a mean survival of <24 months for the SoC arm, and in all extrapolations pembrolizumab offered a survival benefit of >3 months.

Abbreviations: AIC, Akaike information criterion; ALK, anaplastic lymphoma kinase; BIC, Bayesian information criterion; CDF, Cancer Drugs Fund; CS, company submission; EGFR, epidermal growth factor receptor; ERG, Evidence Review Group; ITC, indirect treatment comparison; KM, Kaplan-Meier; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; NSCLC, non-small-cell lung cancer; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; TA, technology appraisal; ToT, time on treatment; TPS, tumour proportion score; TTD, time to death

Source: Adapted from National Institute for Health and Care Excellence, Terms of Engagement: Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer (TA577). London: NICE, 2019[6]

3. CLINICAL EFFECTIVENESS

3.1. Summary of clinical effectiveness evidence and critique

This section provides a structured summary of the clinical effectiveness evidence submitted by the company in support of the use of pembrolizumab in combination with platinum-based chemotherapy (referred to as pembrolizumab combination therapy) for the treatment of adults with untreated metastatic non-squamous NSCLC lacking EGFR- and/or ALK-mutation.

3.1.1. KEYNOTE-189

As in TA557, the source of evidence to support the clinical effectiveness and safety of the use of pembrolizumab combination therapy for the treatment of adults with untreated metastatic non-squamous NSCLC is a Phase 3 randomised controlled trial (RCT), KEYNOTE-189.[1-3] This RCT compared pemetrexed and a platinum-based chemotherapy plus either pembrolizumab (200 mg) or placebo every three weeks for four cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy. Crossover to pembrolizumab monotherapy was permitted among the patients in the placebo-combination group who had verified disease progression. The primary end points were overall survival (OS) and progression-free survival (PFS) as assessed by blinded, independent central radiologic review. Summary study characteristics are provided in Table 4.

Table 4: Summary study characteristics KEYNOTE-189

Trial ID	Phase Study design	Population	Outcomes	Intervention	Comparator
KEYNOTE-189 (NCT02578680)	Phase 3 Randomised, double blind	Adults with advanced or metastatic non-squamous NSCLC; no EGFR or ALK; ECOG ≤1	**Primary:** OS, PFS **Secondary:** ORR, AEs, HRQoL, DOR	Pembro + CT[a] (n=410)	CT[b] (n=206)

Abbreviations: AEs, adverse events; ALK, anaplastic lymphoma kinase; AUC, area under the curve; CT, chemotherapy; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; Pembro, pembrolizumab; PFS, progression free survival; Q3W, every 3 weeks; vs, versus

Notes:

[a] Pembro 200 mg + pemetrexed 500 mg/m^2 and cisplatin (75 mg/m^2) or carboplatin (AUC 5 mg/mL/min) Q3W for 4 cycles, followed by pembro + pemetrexed. Treatment with pembro continued until 35 study treatments had been administered or one of the discontinuation occurred

[b] Saline placebo + pemetrexed 500 mg/m^2 and cisplatin (75 mg/m^2) or carboplatin (AUC 5 mg/mL/min) Q3W for 4 cycles, followed by saline + pemetrexed. Treatment with saline placebo continued until 35 study treatments had been administered or one of the discontinuation occurred

Source: Gandhi et al., 2018[2]

As none of the information on study methodologies, statistical analyses and quality assessment has changed since TA557, the ERG has not included a summary or critique of these aspects in this report. This report instead focuses on the updated clinical effectiveness results.

Data from an interim analysis (IA) (data cut-off date 08 November 2017) from KEYNOTE-189 study formed the evidence base for the company submission in TA557 (CS1).[4] In CS2, the company provided data from the final analysis (FA) of the KEYNOTE-189 trial (data cut-off date of 20 May 2019 [database lock date of [redacted].[1] At the FA data cut-off date, patients had a median duration of follow-up of 18.8 months, an additional 8.3 months compared to CS1 (the point of CDF entry). Although pembrolizumab has been made available within the National Health Service (NHS) through the CDF since January 2019 (refer to CS2 [CDF Review Document A, Table 2]), no clinical effectiveness and safety data based on UK clinical practice have been provided in this submission.

Results from the FA are presented for the intention-to-treat (ITT) population. In Table 5, the ERG has reported the main findings of survival analyses (both PFS and OS) from the interim analysis (IA)3 alongside the final analysis (FA) from KEYNOTE-189[1] (see also Figure 1 and Figure 2 [taken from CS2 [Cancer Drug Fund Review Document A, Sn A6]). As reported in CS1, time on treatment (ToT) was [redacted] for the pembrolizumab combination compared with control (Table 6).[1] Data for other outcomes were not in scope – objective response rate (ORR), duration of response (DoR), and safety.

At data cut-off (20 May 2019), one of the 206 patients in the control arm continued on control treatment. Of the remaining 205 patients, 84 eligible patients with disease progression had crossed over to pembrolizumab monotherapy within the study and an additional [redacted] patients received a PD-1 antibody (pembrolizumab or nivolumab) as subsequent therapy outside of the study protocol, resulting in an overall crossover rate of [redacted] % ([redacted]). In TA557, the company adjusted for additional benefit of pembrolizumab monotherapy in patients who switched from the control arm in KEYNOTE189 and who would not be eligible to do so in UK practice. In response, the ERG commented that the adjustment was appropriate and results were largely unchanged.

In this CDF review, the company considered that it was not necessary to model for crossover in the current submission since second-line treatment with immunotherapy is now standard of care (SoC) in the UK for patients regardless of PD-L1 expression levels. In its clarification response, the company added further detail, noting that atezolizumab monotherapy (TA520) was made

available in the UK in May 2018 as a second-line treatment option for patients irrespective of PD-L1 expression levels. Therefore, subsequent treatment switches from the control arm are likely to occur in UK clinical practice since a PD-L1/PD-1 inhibitor is available across all PD-L1 expression levels. Therefore, treatment switches form a relevant part of the analysis of OS, and it is not necessary to adjust for these treatment changes, in this current submission, since these treatment changes are representative of realistic treatment patterns in the clinic (refer to Clarification Response A4). The ERG noted, however, that this requires an assumption of exchangeability of effect at second-line between pembrolizumab and atezolizumab monotherapies. While the ERG has not seen evidence to support this assumption, it regards that in the absence of limited data, this is likely reasonable.

Table 5: Analysis of OS and PFS (ITT population)

Data cut-off date	**08 November 2017**		**20 May 2019**	
Outcome	**PBR + CT (n=410)**	**Control (n=206)**	**PBR + CT (n=410)**	**Control (n=206)**
Median follow-up (range)	10.5 mths (0.2, 20.4 mths)		18.8 mths	
OS				
Median, mths (95% CI)[a]	Not reached	11.3 (8.7, 15.1)	22.0 mths	10.6mths
HR, mths (95% CI)[b]	0.49 (0.38, 0.64) p<0.00001		0.56 (0.46, 0.69) [redacted][c]	
OS rate % (95% CI)				
at 6 mths[a]	[redacted]	[redacted]	[redacted]	[redacted]
at 9 mths[a]	[redacted]	[redacted]	NR	NR
at 12 mths[a]	69.2 (64.1, 73.8)	49.4 (42.1, 56.2)	69.8 [redacted]	48.0 [redacted]
at 18 mths[a]	.	.	[redacted]	[redacted]
at 24 mths[a]	.	.	45.7 [redacted]	27.3 [redacted]
at 30 mths[a]	.	.	[redacted]	[redacted]
PFS (BICR assessment)[d]				
Median, mths (95% CI)[a]	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)	9 mths	4.9 mths
HR, mths (95% CI)[b]	0.52 (0.43, 0.4) p<0.0001		0.49 (0.41, 0.59) [redacted]	
PFS rate % (95% CI)				
at 6 mths[a]	[redacted]	[redacted]	[redacted]	[redacted]
at 9 mths[a]	[redacted]	[redacted]	NR	NR
at 12 mths[a]	34.1 (28.8, 39.5)	17.3 (12.0, 23.5)	39.4 [redacted]	17.6 [redacted]
at 18 mths[a]	.	.	[redacted]	[redacted]

Data cut-off date	08 November 2017		20 May 2019	
Outcome	**PBR + CT (n=410)**	**Control (n=206)**	**PBR + CT (n=410)**	**Control (n=206)**
at 24 mths[a]	.	.	[redacted]	[redacted]
at 30 mths[a]	.	.	[redacted]	[redacted]

Abbreviations: CDF, Cancer Drugs Fund; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, intention to treat; mths, months; OS, overall survival; PFS, progression-free survival; TA, technology appraisal

Notes:

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

[b] Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/current)

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

[d] Blinded independent central review (BICR) assessment. Results of a sensitivity analysis based on investigator assessment (rather than BICR) per RECIST 1.1 were consistent with the results of the primary analysis (BICR assessment). These results were presented by the company in an Appendix to its submission (refer to CS2, Appendix 2).

Source: Data on File, 2018;[3] Gandhi et al., 2018;[2] Data on File, 2019[1]

Figure 1: Kaplan-Meier estimates of OS

Notes:

In clarification, the ERG requested the company reproduced extrapolated curves in the economic model, placing Kaplan-Meier data on top of the extrapolations. The Kaplan-Meier data utilised in the model showed extra follow-up. Refer to Figure 3 (Section 4.1.5.1) (also refer to Clarification Response Figures 12 to 14)

Source: CS2 (Cancer Drug Fund Review Document A, Sn A6, Figure 1)

Figure 2: Kaplan-Meir estimates of PFS Based on BICR Assessment per RECIST 1.1 (ITT population)

Notes:

In clarification, the ERG requested the company reproduced extrapolated curves in the economic model, placing Kaplan-Meier data on top of the extrapolations. The Kaplan-Meier data utilised in the model showed extra follow-up. Refer to Figure 7 (Section 4.1.5.2) (also refer to Clarification Response Figures 15 to 17)

Source: CS2 (Cancer Drug Fund Review Document A, Sn A6, Figure 2)

Table 6: Analysis of time on treatment

Data cut-off date	**20 May 2019**	
Outcome	**PBR + CT (n=405)**	**Control (n=202)**
ITT population		
N days on therapy, median (range)	[redacted]	[redacted]
N cycles, median (range)	[redacted]	[redacted]
N administration by dose regimen ASaT population – cisplatin/pemetrexed		
N	294	145
Pembrolizumab median (range)	[redacted]	NA
Placebo median (range)	NA	[redacted]
Pemetrexed median (range)	[redacted]	[redacted]
Carboplatin n median (range)	[redacted]	[redacted]
N administration by dose regimen ASaT population – carboplatin/pemetrexed		
N	111	57

Data cut-off date	20 May 2019	
Outcome	**PBR + CT (n=405)**	**Control (n=202)**
Pembrolizumab median (range)	[redacted]	NA
Placebo median (range)	NA	[redacted]
Pemetrexed median (range)	[redacted]	[redacted]
Cisplatin n median (range)	[redacted]	[redacted]

Abbreviations: ASaT, all subjects as treated; CDF, Cancer Drugs Fund; CT, chemotherapy; ITT, intention-to-treat; N, number; PBT, pembrolizumab; TA, technology appraisal

Notes:

For subjects who crossed over to PBR from the control group, doses administered after crossover are excluded

Source: Data on File, 2019[1]

Results reported in Table 5 suggest similar survival outcomes with the most updated follow-up data compared to those presented in TA557:

- Pembrolizumab in combination with chemotherapy, when compared to placebo in combination with chemotherapy, reduces the risk of death by 44% in patients with previously untreated metastatic non-squamous NSCLC without EGFR or ALK mutations (Table 5 and Figure 1).[1]
- Pembrolizumab in combination with chemotherapy, when compared to placebo in combination with chemotherapy, reduces the risk of disease progression or death by 51% in patients with previously untreated metastatic non-squamous NSCLC without EGFR or ALK mutations (Table 5 and Figure 2).[1]

Results for the subgroup of patients with programmed death-ligand 1 (PD-L1) positive tumour proportion score (TPS) ≥50% were relevant for the comparison of pembrolizumab combination therapy with pembrolizumab monotherapy in CS1 (TA557). These results were not reported by the company in CS2 but were requested and obtained from the company during clarification (refer to Clarification Response A1). No further subgroup data were presented by the company in CS2. However, the ERG considered that the relevant population had been recognised in presentation of the FA data in the ITT population.

3.1.2. Summary and critique of evidence synthesis

3.1.2.1. Pembrolizumab combination vs other chemotherapy treatments

The company did not present a comparison of pembrolizumab combination with other chemotherapy treatments ((docetaxel, gemcitabine, paclitaxel or vinorelbine as monotherapy), with carboplatin or cisplatin, with or without pemetrexed maintenance therapy) by means of an NMA or an updated systematic literature review (SLR). The company's justification was that the results of the NMA, in CS1[4] at the point of CDF entry, showed no statistically significant difference between the platinum doublet chemotherapy interventions commonly used in UK clinical practice. The results showed pembrolizumab combination was beneficial for OS and PFS compared to the other platinum doublet chemotherapy interventions.[4] While the ERG accepted the rationale provided, it also noted that the degree to which new evidence would have changed the conclusions of the NMA was unclear. The ERG also acknowledged the clinical feedback given at the time of TA557, that platinum + docetaxel, platinum + paclitaxel, and platinum + paclitaxel + bevacizumab were not commonly used in UK clinical practice.[4] The company further argued that in the appraisal of atezolizumab (TA520), pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was considered the relevant comparator for the for first-line non-squamous NSCLC population by the CDF clinical lead.[7]

3.1.2.2. Pembrolizumab combination vs pembrolizumab monotherapy

In response to Clarification Question A1, the company presented an updated indirect treatment comparison (ITC) to compare pembrolizumab combination therapy with pembrolizumab monotherapy in patients with PD-L1+ TPS ≥50%.[8] This comparison was anchored by a common comparator of pemetrexed with carboplatin or cisplatin. At variance with the analysis presented in TA557, four trials (KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, KEYNOTE-021G) were used, thus integrating all available trial evidence.[8] Methods used to undertake the ITC were appropriate, and consisted of selection of similar sets of patients from all three trials, reweighting of observations to generate covariate balance across arms and between trials, re-estimation of treatment effects within trials using Cox proportional hazards regressions, and then subtraction of trial-level summary effects to generate the indirect estimate of relative effectiveness. The ERG noted that while the number of characteristics used to generate the reweighting was sparse, these were clinically relevant and good balance was achieved within and across trials on these characteristics.

Findings for this new ITC suggested that pembrolizumab combination therapy offers a numerical, but not statistical, improvement in OS as compared to pembrolizumab monotherapy (HR=[redacted]).[8] In contrast, pembrolizumab combination therapy does appear to offer a benefit in PFS as compared to pembrolizumab monotherapy (HR=[redacted]).[8] Tests of proportional hazards assumptions were not presented, so the ERG could not assess how appropriate these HRs are as summary estimates. While this assumption appeared broadly appropriate for analyses of OS, analyses of PFS suggest crossing survival curves in the comparison of pembrolizumab monotherapy with the anchor treatment. The ITC of PFS may thus be regarded with some caution.

3.2. Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

3.3. Conclusions of the clinical effectiveness section

The evidence presented in CS2 was from the KEYNOTE-189 trial which included patients with untreated, metastatic non-squamous NSCLC without EGFR or ALK positive mutation.

The FA (ITT population) reinforced the IA data presented in CS1 (TA557) indicating that pembrolizumab combination therapy is likely to offer a survival benefit in comparison to placebo combination therapy (standard of care, chemotherapy).

Subgroup data were presented for patients with PD-L1+ TPS ≥50% during the clarification step. This was relevant for the combination of pembrolizumab combination therapy with pembrolizumab monotherapy. Broadly, the ERG considered the ITC was fit for purpose and noted a numerical improvement in OS and a potential benefit in respect of PFS; however, it advised that the latter be treated with caution. No other subgroup data were presented in CS2; however, the ERG believed that the relevant population for the decision problem was captured in the FA (ITT population).

No comparison was presented versus “other chemotherapy”. The ERG accepted the company’s rationale but noted that it was unable to comment on the degree to which new evidence would have changed the conclusions of the NMA. The ERG also acknowledged the clinical opinion received in TA557 that “other chemotherapy” was not commonly used in UK clinical practice, [4] and the company’s further argument that during the appraisal of atezolizumab (TA520), that pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was considered the

relevant comparator for the for first-line non-squamous NSCLC population by the CDF clinical lead.[7]

4. COST-EFFECTIVENESS

4.1. Summary and critique of company's submitted economic evaluation by the ERG

This section provides a summary and structured critique of the economic evidence submitted by the company in support of pembrolizumab combination for the treatment of people with previously untreated non-squamous non-small-cell lung cancer. The key component of the economic evidence updated as part of this CDF review is the survival analysis provided from the final analysis of KEYNOTE-189.

The company submitted four different economic models. The differences between these models are summarised in Table 7.

Table 7: Models submitted by the company alongside CS2

Model number	Label	Received	Key differences
1	ID1584 pembrolizumab MSD Submission CEM (ID1584) (ACIC) - FA - ITT	Submission	- Main population - No subgroups - FA data
2	ID1584 pembrolizumab MSD Submission CEM (ID1173) (ACIC) - IA1 - ERG assumptions	Submission	- Main population - ERG preferences from TA557 - FA data
3	ID1584 MSD submission pembrolizumab combination FA ITT and subgroup (noACIC)	Clarification	- Main population - ≥50% TPS subgroup - Pembrolizumab monotherapy as a comparator - FA data
4	ID1584 MSD model 189 FA ITT and GE50 IA1 added 03022020KM (ACIC)	Clarification	- IA1 data - FA data - Main population - ≥50% TPS subgroup - Pembrolizumab monotherapy as a comparator

Key: ERG, evidence review group; FA, final analysis; IA1, interim analysis 1; ITT, intention-to-treat; TPS, tumour-proportion score

Given the concentration of this appraisal is the review of TA557,[4;5] this report focuses on outlining key, important changes to the economic evidence submitted and differences from TA557. Since CS1, the company has adapted some model settings. The company now considers log-logistic models for OS, Weibull models to extrapolate PFS and exponential models for time-on-treatment (TOT). The company have also adapted their approach to considering HRQoL with an approach presented by the ERG in TA557.

The company has presented a base case ICER [redacted] in CS2 and a corresponding probabilistic ICER of [redacted]. After reviewing the submission and the new economic evidence available, the ERG agrees that pembrolizumab is still likely to offer a benefit to people receiving treatment over the current SoC, with increased PFS and OS. The ERG considers that there is still some uncertainty in the extrapolations for OS in particular, and that the corresponding extrapolations should be interpreted with caution. When testing the structural uncertainty within the model and varying the parametric survival curve selection through various scenarios, the model ICER frequently exceeded £50,000 per incremental QALY gained.

Of the analyses presented by the company and the ERG (outlined in Sections 5 and 6), the ICER is predominantly higher than £50,000 per QALY gained but has a broad range from [redacted] to above [redacted].

4.1.1. Model structure

The company submitted an economic model constructed in Microsoft Excel® to assess the cost-effectiveness of pembrolizumab in comination with pemetrexed and platinum-based chemotherapy (referred to as pembrolizumab combination therapy) relative to SoC for people with previously untreated non-squamous NSCLC. The model had the same structure as was previously submitted as part of TA557;[4;5] a three-state partitioned survival model, with the three states being progression-free disease, progressed disease and death. Please refer to the original committee papers (TA557) for more detail.[4;5]

The key element of uncertainty underpinning the economic modelling presented in TA557 (CS1) was the extent of OS benefit with comparing pembrolizumab combination therapy with SoC.[4-6] The primary source of data collection to help resolve this uncertainty was the ongoing clinical study, KEYNOTE-189.[1-3]

The model submitted alongside this appraisal follows the same model structure, with the main differences between the IA1 model and the final analysis (FA) model being:

- The use of additional follow up data from the KEYNOTE-189 trial (referred to as the final analysis).
- The approach to utilities, which is slightly different to the base-case approach used at the time of the original appraisal.
- The selection of the parametric survival models for OS, PFS and ToT.

Otherwise approaches, underlying model assumptions, and estimates remained largely the same.

4.1.2. Population

The model considers adults with untreated, metastatic non-squamous NSCLC whose tumours have no EGFR or ALK positive mutation. At the point of appraisal in TA557 (CS1), the model considered three subgroups based on different levels of PD-L1 expression:

- <1% TPS
- 1%≤TPS≤49%
- ≥50% TPS.

Given the third subgroup (≥50% TPS) was relevant to TA557 to compare pembrolizumab combination with pembrolizumab monotherapy, the ERG requested that the company present subgroup data in clarification (refer to Clarification Question and Response A1[8]). Results of this analysis are presented in Section 3.1.2.2 and Section 5.2.

No further subgroups are presented by the company in the revised submission. Based on the decision problem and the current SoC, it is the ERG's belief that the omission of these subgroups should not affect the decision-making process and the relevant subgroup which impacts the treatment pathway has been recognised and included within the company FA model.

4.1.3. Interventions and comparators

The cost-effectiveness analysis compared pembrolizumab combination therapy to pemetrexed with carboplatin or cisplatin (i.e. SoC) in the wider population. Within the subgroup analysis (PD-L1+ NSCLC with a TPS ≥50%) pembrolizumab combination therapy was compared to pembrolizumab monotherapy.

The original scope as part of TA557 included other chemotherapy treatments as a comparator in the wider population (docetaxel, gemcitabine, paclitaxel or vinorelbine as monotherapy, with carboplatin or cisplatin, with or without pemetrexed therapy).[4] In the FA model submitted by the company, this comparison was excluded. The company rationale for not comparing pembrolizumab to the "other chemotherapy" was that no significant difference was observed between platinum doublet chemotherapy interventions commonly used in clinical practice. While the ERG accepted the rationale provided, it also noted that the degree to which new evidence would have changed the conclusions of the NMA was unclear. The ERG also acknowledged the clinical feedback given at the time of TA557, that platinum + docetaxel, platinum + paclitaxel, and platinum + paclitaxel + bevacizumab were not commonly used in UK clinical practice.[4] The company further argued that in the appraisal of atezolizumab (TA520), pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was considered the relevant comparator for the for first-line non-squamous NSCLC population by the CDF clinical lead.[7]

4.1.4. Perspective, time horizon and discounting

The company approach to the perspective, time horizon and discounting was the same as that submitted in TA557. The model considered a NHS and PSS perspective, had a 20-year (effectively life-time) time horizon, with costs and benefits discounted at 3.5% per year.[4]

Within the original appraisal the company noted that a 20-year time horizon was appropriate as 0% of people in the pembrolizumab combination arm and 0% in the SoC arm were still alive after that period. The committee and the ERG considered this appropriate and no further alternative scenarios were explored in relation to the model time horizon.

Within the revised economic model (submitted alongside the udpated company submission [CS2]) after 20 years, 3% people in the pembrolizumab arm and 1.3% in the chemotherapy arm are alive after this period. Given these higher proportions, the ERG considers that either the time-horizon is not sufficiently long enough to capture all relevant treatment effects (as outlined in the NICE methods guidance),[9] or alternatively that the OS extrapolations considered within the base case may be too optimistic. OS extrapolation is further discussed in Section 4.1.5.1. The time horizon and the OS extrapolation are explored in sensitivity analyses presented by the ERG (Section 6).

4.1.5. Treatment effectiveness and extrapolation

The company's base-case model relies on patient-level data from the KEYNOTE-189 trial. As outlined in Section 3.1.1,at the final analysis cut-off date, patients had a median duration of follow-up of 18.8 months, an additional 8.3 months compared to the submission presented at the point of CDF entry.

As the follow-up period within the trial was shorter than the required length of the economic evaluation and all events within the trial were not experienced, extrapolation of outcomes was necessary. Data informing the extrapolations were based on the final analysis of KEYNOTE-189 and included for OS, PFS and TOT.

In CS1, parametric survival models were fitted to interim analysis data from the pivotal KEYNOTE-189 study (data cut: November 2017).[4] As part of the CDF review, updated data from KEYNOTE-189 (data cut: May 2019) were used to inform three modelled survival curves: OS, PFS, and ToT. An overview of the updated data was provided by the company in its submission (refer to CS2 [CDF Review Document A, Section A.8]).

4.1.5.1. Overall survival

Based on the interim analysis KEYNOTE-189 data, the committee stated a preference for extrapolations based on either a generalised gamma or log-logistic model, which were applied independently to both arms. When re-fitting models to the updated KEYNOTE-189 data, the company has stated a preference for a log-logistic model, based on inspection of its visual fit to the Kaplan-Meier curves and interpretation of statistical goodness-of-fit scores (i.e. Akaike's and Bayesian Information Criteria [AIC and BIC]). The company also noted that the ERG previously stated a preference for the log-logistic model over a piecewise approach using the Kaplan-Meier curve followed by an exponential model (at Week-28).

At clarification stage, the company provided additional justification for the choice of model. As part of this response, the company noted that *"Following the recommendation from the DSU, the same functional form was selected for the separate parametric models according to that fitting most closely the data overall."* The ERG noted that in several of NICE's previous assessments of cancer immunotherapies, a different functional form has been selected for the intervention versus the (non-immunotherapy) comparator based on the expectation of a different shape to the survival curve (e.g. in TA517[10] and TA400[11]). Therefore, while models with the same functional form may be appropriate, it may also be of interest to consider models with differnet functional forms to best illustrate the pattern of survival for different types of treatments.

In Table 11 CS2 (CDF Review Document A), the statistical goodness-of-fit scores are presented. The scores demonstrate that the log-logistic model fitted to the pembrolizumab combination arm is ranked five out of six for AIC, with a score of 3,058.3. The statistically best-fitting model (Weibull) has an AIC score of 3,053.4, meaning use of a log-logistic model leads to a ΔAIC of 4.9 points. Burnham and Anderson offer a 'rule of thumb' which states that models with a $4 \leq \Delta AIC \leq 7$ have *"considerably less support"* than models with $\Delta AIC \leq 2$.[12] Based on this interpretation, the ERG highlights the importance of considering alternative models for OS.

Of the models provided by the company, the ERG considered both the log-logistic and generalised gamma parameterisations suitable candidates to inform the cost-effectiveness analysis. To compare these models, the ERG has produced Figure 3 which shows that the extrapolations for the SoC arm are similar using either functional form, yet for the pembrolizumab combination arm the extrapolations differ markedly (e.g. five-year survival is 19.8% for the log-logistic model, versus 12.1% for the generalised gamma model). Both of these models yield estimates of five-year OS that exceed the expected range for the SoC arm (5-11%, as discussed in the TA557 FAD).[4]

As acknowledged in Section 5.1.4, the selection of the log-logistic curve for OS results in 3% of people being alive in the pembrolizumab combination arm by the end of the modelled time horizon, which raises questions to the appropriateness of applying a 20-year time horizon and the extrapolation approach. When considering the generalised gamma curve, this value is reduced to 0.62%, and therefore the generalised gamma curve may represent a more appropriate extrapolation in light of the time horizon and expected long-term outcomes.

Figure 3: Comparison of log-logistic and generalized gamma models for overall survival

Key: Gen gamma, generalized gamma; KM, Kaplan-Meier; Pembro, pembrolizumab combination; SoC, standard of care.

Note(s): Inset illustrates difference in projections in the longer-term. These projections are based on the company base-case settings, including a treatment waning effect applied at 5 years. The waning effects for each of the pembrolizumab combination curve are based on the equivalent functional form for the SoC curve.

Source(s): Produced via the company's economic model.

The generalised gamma model has a ΔAIC of 2 points for the pembrolizumab combination arm, and so based on the 'rule of thumb' proposed by Burnham and Anderson, this model has *"substantial support"*.[12] Furthermore, the generalised gamma model includes the lognormal, Weibull, and exponential models as special cases; and so inspection of this model may reveal more information concerning the underlying pattern of survival for each arm:

- For the pembrolizumab combination arm, the generalised gamma model provides a fit very similar to that of the Weibull model (refer to CS2 [CDF Review Document A, Figure 3])
- For the SoC arm, the generalised gamma model provides a fit more aligned with the lognormal model versus the Weibull model (refer to CS2 [CDF Review Document A, Figure 4]).

This finding suggests that there is evidence of a different pattern in survival across both treatment arms, and so models with alternative functional forms may be relevant to consider.

Based on the explanation provided above, the ERG believed the generalised gamma extrapolation was equally important to consider alongside the log-logistic function, and should not be discounted. The generalised gamma provides a better statistical fit to the KEYNOTE-189 trial data, as well as plausible long-term extrapolation. Accordingly, the ERG opted to select the generalised gamma models for both treatment arms to inform its base-case OS projections.

The ERG highlighted that the company projections include a treatment waning effect (TWE), which is imposed at five years. Using this model setting, the estimated hazard of death for patients on the pembrolizumab combination arm is assumed to be equal to the SoC arm after five years. If the TWE is disabled in the base-case analysis, the ICER decreases from [redacted] to [redacted]. However, should generalised gamma models be applied for both arms, removal of the TWE causes the ICER to increase from [redacted] to [redacted]. Using a combination of a generalised gamma model for the pembrolizumab combination arm, and a log-logistic model for the SoC arm, the ICER is [redacted] with the TWE, and [redacted] without the TWE. These results, which appear to lack face validity when the generalised gamma curve is selected for pembrolizumab, is a direct result of the extrapolated curves which produce a lower hazard at five years for the SoC arm than the pembrolizumab arm. Hence, applying a TWE in fact increases survival with for pembrolizumab.

In the TA557 FAD,[5] it is stated that the committee concluded scenarios that included a TWE applied at a time point between three and five years from the start of treatment were appropriate for decision making. With this in mind, the ERG conducted an additional sensitivity analysis to explore the relationship between the TWE and the ICER, by varying this time point between three and five years. The outcome of this analysis is presented in Figure 4. As can be seen, the ICER is above [redacted] for any timepoint lower than five years (per the company base-case analysis). If the treatment effect is modelled to apply until three years (the lower bound of the range stated in the FAD), the ICER increases to [redacted].

Figure 4: Relationship between TWE and ICER

Key: ICER, incremental cost-effectiveness ratio; TWE, treatment waning effect.
Note(s): TWE refers to the time point at which the treatment effect of pembrolizumab is assumed to dissipate.
Source(s): Produced via the company's economic model.

Given there is uncertainty in the timepoint at which a TWE should be applied, and treatment with pembrolizumab stops at two years, the ERG implemented a new scenario which applied a TWE gradually from the point of discontinuation up until the upper bound outlined in TA557 (five-years). This gradual effect happens linearly with a weighted hazard being produced at each cycle, to generate an adjusted pembrolizumab combination OS estimate. Figure 5 illustrates this approach in comparison to the company base case. Further ERG analyses were also explored which apply the gradual approach until 10 years (the upper bound provided in company scenario analysis (refer to CS2 [CDF Review Document A, p.38]). Applying a gradual TWE approach avoids a sudden change in hazards that may sometimes be seen with applying a TWE to extrapolations of immuno-oncologies (IOs) versus chemotherapy. The ERG base case approach assumed a generalised gamma for both treatment arms and applied a gradual TWE between two and five years.

Figure 5: Treatment waning effect – gradual approach

Key: SoC, standard of care.

Note(s): This shows the weighting of each of the hazards applied to create an adjusted pembrolizumab TWE OS curve. The left shows the base case approach provided by the company and the right shows a gradual effect applied between years 2 to 5.

Source(s): Produced via the company's economic model.

4.1.5.2. Progression-free survival

The company provided a piecewise approach wherein the Kaplan-Meier curve is followed up until Week 21, followed by a Weibull model. In the original CS, the ERG noted that the extrapolation of PFS did not affect model results (as both costs and utility values were not driven by progression status). However, in the updated model, progression status informs utility values, and thus this approach impacts cost-effectiveness results (see Section 4.1.6 for more information concerning utility values).

The company argued that *"a change in the hazard was observed in Week 21 and a piecewise apporoach seemed appropriate"*. At clarification stage, the company provided additional evidence concerning the rationale for using a piecewise approach. The company provided Chow tests to demonstrate the estimated change in hazards over time (refer to Clarification Question A4 response[8]). The ERG noted that hazards are not observed, as the estimated hazard of death may only be inferred through analysis of survivor data. This means that any

attempt to quantify the change in the hazard of death over time is uncertain, and requires careful consideration.

For context, in the KEYNOTE-189 study, patients were assessed for progression at six and 12 weeks, followed by imaging every nine weeks until Week 48 and every 12 weeks for the remainder of the study (refer to CS1, Section B.2.3[4]). Consequently, the ERG did not consider it a coincidence that Week 21 (i.e. 12 + 9) appeared to be a relevant time point at which the hazard of experiencing a PFS event changes (given that this corresponds to the approximate time point at which patients would be assessed for progression).

Moreover, when superimposing the timing of progression assessments on the company's Chow test plots, it oulde seen that many of the peaks and troughs in the plot roughly corresponded to time points where progression was assessed (Figure 6), though the global maximum (highest point) is not consistent for both arms and the 21-week selection is based on the SoC global maximum. In addition, it is important to note that KEYNOTE-189 was randomised 2:1, and so the decision to impose a cutpoint at 21 weeks has been made based on data for approximately one-third of the study population.

Figure 6: KN189 FA – PFS Chow Test (edited to show progression assessments)

Key: SoC, standard of care.
Note(s): Red vertical lines demonstrate timing of progression assessments in the KEYNOTE-189 trial.
Source(s): Adapted from company clarification question A4 response.

The ERG would have preferred to explore the option of using a fully parametric approach to model PFS as well as the piecewise approach adopted by the company. A fully-parametric approach would avoid the need to specify a given cut-point, as the ERG did not consider the evidence presented by the company to be sufficient to justify a specific cut-point. In the piecewise approach used by the company, the estimated PFS curve is assumed to be fixed to Week 21, and so the uncertainty in the PFS curve (explored in probabilistic analysis) is only considered after this time point. In addition, setting the cut-point to either 11 or 31 weeks (options included within the company model), cause the ICER to increase ([redacted]). A comparison of these models is provided in Figure 7.

Figure 7: Comparison of piecewise models for progression-free survival

Key: KM, Kaplan-Meier; Pembro, pembrolizumab combination; SoC, standard of care; w, weeks.
Note(s): Inset illustrates difference in projections in the short-term. The time in weeks corresponds to the cut point used to switch from the KM curve to the Weibull model.
Source(s): Produced via the company's economic model.

In spite of the concerns raised by the ERG above, the base-case projections (KM + Weibull) provided by the company appear to provide a reasonable fit to the Kaplan-Meier curves, and are therefore considered a suitable basis for informing decision making, alongside the models that consider alternative cut points.

4.1.5.3. Time-on-treatment

In the original CS, the company used an exponential model for the pembrolizumab combination arm, and a Weibull model for the SoC arm. In the updated model, an exponential model was used for both treatment arms. By using an exponential model, the company assumed proportional hazards between the two arms for this outcome (given that the exponential model considers a constant hazard over time). No evidence was provided by the company to support the proportional hazards assumption.

The base-case projections are presented in Figure 8. While the ERG considered the exponential models to provide a reasonable fit to the Kaplan-Meier curves for both arms, there are some important considerations. Firstly, the model for pembrolizumab combination slightly under-estimates the Kaplan-Meier curve between one and two years, yet this is a feature of the majority of the models fitted by the company (refer to CS2 [CDF Review Document A, Figure 9]). Secondly, it was also unclear to the ERG why the rate of discontinuation could be assumed constant, when considering a combination of three components, one of which is assumed to be withdrawn at exactly two years.

Figure 8: Time-on-treatment extrapolations (company base-case analysis)

Key: KM, Kaplan-Meier; Pembro, pembrolizumab; Pembro combi, pembrolizumab combination; SoC, standard of care.

Note(s): Dotted line shows company assumption that all patients with stop treatment with pembrolizumab at 2 years, but continue the pemetrexed + platinum chemotherapy components of the regimen.

Source(s): Produced via the company's economic model.

In Table 13 of CS2, the statistical goodness-of-fit scores for TOT are presented. The scores demonstrate that the generalised gamma was the best fitting model based on AIC, and exponential based on BIC. The same relationship was seen in the models fit to the SoC arm. Table 5 reports the AICs and BIC statistics. Overall there was a ΔBIC between the exponential and generalised gamma of <2.5 for both arms, while the difference between the exponential and generalised gamma when considering the ΔAIC was >5. Therefore although similar visually, based on the AIC/BIC statistics acknowledged in Section 4.1.5.1, the ERGs preference was to adopt a generalised gamma curve for both treatments.

Table 8: AIC/BIC statistics for ToT

Function	**Pembrolizumab combination**				**SoC**			
	AIC		BIC		AIC		BIC	
Exponential	3770.2	5.4	3774.3	2.5	1737.1	5.9	1740.4	0.8
GenGamma	3764.8		3776.8		1731.2		1741.2	

Key: AIC, Akaike information criterion; BIC, Bayesian information criterio; SoC, standard of care; ToT, time on treatment

Source(s): Obtained from the company submission (CS2, CDF Review Document A, Table 13])

The ERG was concerned with how the company modelled TOT in that the Kaplan-Meier presented (refer to Clarification Response, Figure 32[8]) represented those receiving treatment with pembrolizumab combination therapy. It is the ERGs understanding that patients may discontinue pembrolizumab, or chemotherapy but this does not necessarily have to be both. Consequently, depending on how ToT has been derived from the KEYNOTE-189 data there is a risk that the costs of treatment have been under or overestimated in the economic model (depending on how the Kaplan-Meier curves would look when split by the treatment received). The ERG would have preferred an approach which considered two sets of parametric survival models fit to the KM data; one for pembrolizumab and one for the remainder of the combination. This would have avoided the potential for bias. Despite this, the ERG acknowledge that this was not considered at the time of the original submission in TA557.

4.1.6. Health-related quality of life

Table 14 of the company submission (CS2) outlined the key model settings and assumptions (refer to CS2 [CDF Review Document A, p.38]). Within this table, it was noted that the approach to utilities had changed since CS1. The base case now incorporated utilities based on time-to-death with an additional decrement applied for progression. The company outlined that this was

based on clinical expert opinion received throughout TA557, and the committee preferences at the point of CDF-entry.[4;5]

As part of TA557 two methods were explored which incorporated both progression status and time-to-death within the estimation of utilities:

1. Progression based utilities with a decrement applied in the last year of life (Approach 1)

2. Time-to-death utilities with a decrement applied to account for progression (Approach 2)

The committee preference at the time of TA557 was Approach 1. As such, the ERG is unclear as to why the company's base-case analysis diverges from this model setting. The economic model is sensitive to the approach incorporated, and incorporating Approach 1 increases the base case ICER by [redacted]. Further to this, as highlighted in Figure 15 of CS2 (CDF Review Document A, p.47), six of the top 20 parameters presented within the one-way sensitivity analysis (OWSA) were related to the utility values applied.

In reviewing the economic models submitted alongside CS2, the ERG noticed that the utility decrement from either method was not varied in sensitivity analysis, meaning that the underlying uncertainty is likely to be underestimated in the sensitivity analyses provided by the company. Further to this, the utilities included within the analysis are varied independently and do not apply a multi-variate distribution. This means that within the OWSA or the probabilistic sensitivity analysis (PSA) it is possible that the parameter values selected will lack face validity; for example, the probabilistic sampled time to death utility for people who die within 30 days may be higher than those who have 180–360 days to live. Alternatively, the OWSA lower bound of the utility applied to people surviving >360 days may be lower than the point estimate for people surviving between 180–360 days, which when varying parameters in isolation lacks face validity. Table 9 highlights where in the OWSA this scenario will appear.

Table 9: Parameter uncertainty explored in OWSA

	Point estimate	Lower bound	Upper bound	Lower bound < another utility point estimate where HRQoL would be anticipated to be better	Upper bound > another utility point estimate where HRQoL would be anticipated to be worse
Pembrolizumab + chemotherapy - utility	0.790	0.632	0.948	✓	

time to death >=360 days					
Pembrolizumab + chemotherapy - utility time to death days [180,360)	0.691	0.5528	0.8292	✓	✓
Pembrolizumab + chemotherapy - utility time to death days [30,180)	0.607	0.4856	0.7284		✓
Pembrolizumab + chemotherapy - utility time to death <30 days	0.397	0.3176	0.4764		
Chemotherapy - utility time to death >=360 days	0.790	0.632	0.948	✓	
Chemotherapy - utility time to death days [180,360)	0.691	0.5528	0.8292	✓	✓
Chemotherapy - utility time to death days [30,180)	0.607	0.4856	0.7284		✓
Chemotherapy - utility time to death <30 days	0.397	0.3176	0.4764		

Key: HRQOL, health-related quality of life

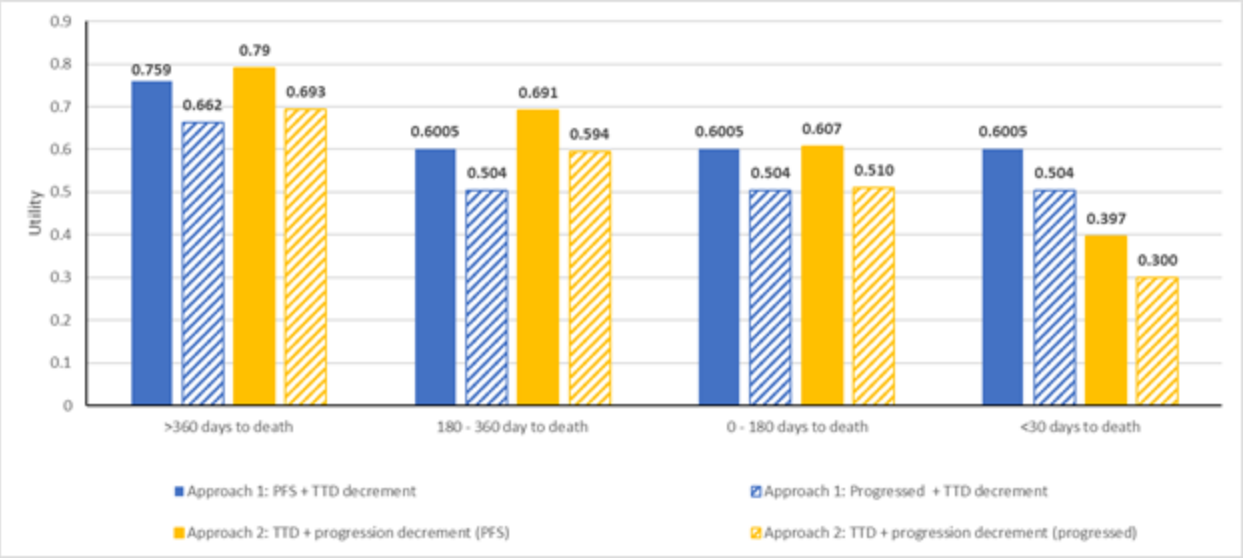
Note(s): The ticks mark all the scenarios in the OWSA where a scenario would arise which may appear to lack face validity when the parameter is varied in isolation. Cells with an X refer to lower or upper bounds where this nuance is not applicable.

Source(s): Produced via the company's economic model

Whilst the ERG is unable to comment on the validity of either method without appropriate clinical insight, both the parameter uncertainty around either method, and the structural uncertainty relating to the method to choose should not be underestimated. Both methods incorporated the two components that clinical experts expressed importance towards; progression and time to death; however, the ERG acknowledges that both approaches have limitations. Notably, the merging of the approaches may double count the effects of progression or being close to death. Secondly, that neither approach has been updated using the KEYNOTE-189 FA data. Consequently, this means the HRQoL informing the health states in CS2 are based on immature data, and is inherently more representative of trial participants where events occurred earlier. The HRQoL impact of progression and time-to-death observed within KEYNOTE-189 may have affected the average utility.

Figure 9 illustrates the two approaches and how that equates to HRQoL concerning hypothetical patients. The figure highlights Approach 2 consistently applies higher utilities than Approach 1, with the only exception being in the last 30 days of life (which across a lifetime horizon would result in very little difference between the two treatment arms).

Figure 9: HRQoL options based on Approach 1 and 2 for combining time-to-death and progression status



Key: PFS, progression-free survival; TTD, time-to-death
Source(s): Produced via the company's economic model.

4.1.7. Resources and costs

To inform drug costs, dosing intensity was taken from the KEYNOTE-189 trial (dosing of the trial is outlined in Section 3.1.1). At clarification stage the company provided the ERG with updated dose intenity from the final analysis. Updated results are presented in Table 10. Overall, although there was little difference, the ERG considers it more appropriate to incorporate the updated dose intensities. These values have therefore been incorporated into the ERG base case. Aside from this, all costs are aligned to CS1 used to inform TA557.[4]

Table 10: Dosing intensity from KEYNOTE-189

	Dosing intensity	
Trial data-cut	**Pembrolizumab**	**SoC**
KEYNOTE-189 interim analysis	95.6%	96.4%
KEYNOTE-189 final analysis	[redacted]	[redacted]

Key: SoC, standard of care

Source(s): Produced based on information provided within the company's economic model and responses received at clarification[8]

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

The results presented throughout this section include the agreed patient access scheme (PAS) for pembrolizumab. They do not include existing agreements for comparators and treatments given in combination with pembrolizumab.

5.1.1. Base case results

The company's base case results for the comparison of cost effectiveness of pembrolizumab combination therapy versus SoC are shown in Table 11. The deterministic ICER was [redacted] per quality adjusted life year (QALY) gained. The mean incremental costs were [redacted] per person and the mean incremental QALYs gained per person was [redacted] over the model time horizon.

Table 11: Base case results (deterministic)

	Costs	QALYs	ΔCost	ΔQALY	ICER
Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Source(s): Company submission (CS2 [CDF Review Document A, A10 and Table 15])

5.2. Company's sensitivity analyses

The scope of this appraisal also included pembrolizumab monotherapy as a relevant comparator for consideration for people whose tumours express PD-L1 with at least a 50% tumour proportion score.

At clarification stage, the company provided results of a subgroup analysis for patients that have a TPS ≥50% to compare pembrolizumab combination to pembrolizumab monotherapy. Table 12 presents the results of this analysis. As outlined in the FAD of TA557,[5] pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% TPS does not meet NICEs end-of-life criteria. This is because survival in this population with the current standard of care (pembrolizumab monotherapy) is above 24 months. As such, an ICER of [redacted] is above the generally considered £20,000 - £30,000 willingness to pay threshold.

Table 12: Subgroup results comparing pembrolizumab combination to pembrolizumab monotherapy in patients with at least a 50% TPS

	Costs	QALYs	∆Cost	∆QALY	ICER
Pembrolizumab monotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year
Source(s): Clarification response[8]

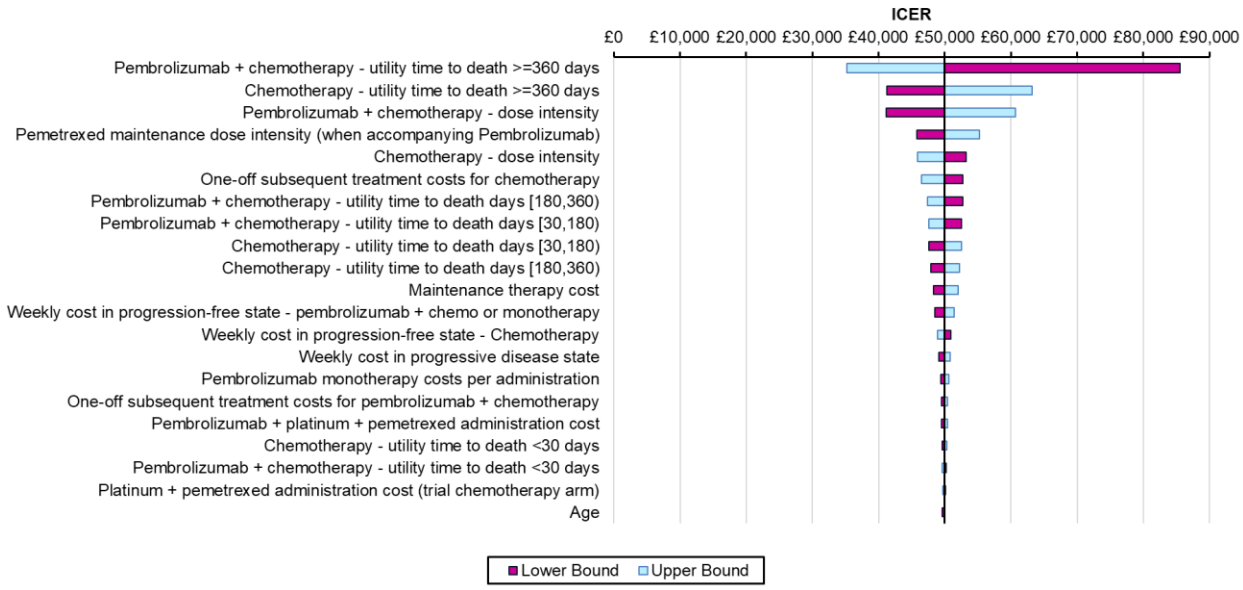
5.2.1. One-way sensitivity analysis

Figure 15 in the company submission (CS2, p.47), presents results of a OWSA, illustrating the impact paramater variation has on the ICER. The results indicated that the model was most sensitive to parameters related to time-to-death utility values.

The ERG believes that some parameters the company consider relevant for inclusion within the OWSA should be omitted. Firstly the inclusion of curve parameters; where there are multiple curve parameters informing parametric model fits, they are instrinsically linked and therefore should not be varied in isolation (as is the case in a OWSA).[13;14] Secondly, discount rates relate to structural uncertainty within the model which should be explored using scenario analysis, not in a OWSA which is used to explore parameter uncertainty.

It could also be argued (as outlined in Section 4.1.6), that the utility values are fundamentally linked and therefore also should not be tested as part of OWSA, however given the importance of testing the uncertainty around utilities, the ERG considers it reasonable to leave these in, but with the acknowledgement that it has limitations. The ERG has therefore explored the results of the OWSA with the curve parameters and discount rates omitted, with results presented in Figure 10. The outcome of this exploratory analysis illustrates that six of the top ten parameters included in the OWSA are related to the utilities values used within the model – emphasising the importance of agreement between the committee and the company about the appropriate Method to utilise within the model to capture HRQoL (see Section 4.1.6).

Figure 10: Tornado diagram - parameters removed by the ERG



Company submission (CS2 [CDF Review Document A, A12 and Figure 15])

5.2.2. Probabilistic sensitivity analysis

Table 16, Figure 13 and Figure 14 in the company submission (refer to CS2 [CDF Review Document A, p.44 – p.46]), report the results of the PSA. Results from the analysis provided an average ICER of [redacted], an [redacted] of [redacted] from the base case result [redacted]). At a willingness to pay threshold of £50,000 pembrolizumab combination has a 16.2% probability of being cost-effective.

5.2.3. Scenario analyses

The company present five key scenarios to explore uncertainty within the model:

- Log-normal curve applied to OS.
- Piecewise extrapolation applied to OS (using the Kaplan-Meiers followed by the log-logistic curves).
- Varying the TWE to three years.
- Varying the TWE to 10 years.
- Applying the alternative combined method of estimating utilities (Approach 1).

As presented in Table 18 of the company submission (CS2, [CDF Review Document A, p.49 – 50]), all scenarios provided increase the ICER compared to the the base case, with one exception - when the TWE is applied from five years in the base case to 10 years. Within the submission the company indicate that the ICER in the scenarios presented are consistently below £50,000 per QALY. Despite the company acknowledging at clarification stage that results of the scenario analyses do in fact result in ICERs consistently above a £50,000 per QALY estimate, the company commented "it should be noted that none of the scenarios presented, provided a significantly high ICER with the highest being under £55,000 per QALY" (refer to Clarification Response, p.49[8]). The company also provided PSA results for each of the scenarios. Results of the PSA were consistently higher than the deterministic results and again consistently above a £50,000 cost per QALY.

The ERG did not consider the scenarios presented to be sufficient enough to fully explore and understand the impact of uncertainty within the model. Further to this, the ERG did not consider the scenarios presented by the company, to which all except one were above a £50,000 willingness to pay threshold and higher than the base case ICER, to be adequate justification as to why pembrolizumab combination therapy may be considered a cost-effective use of NHS resources. As a result, the ERG has explored several further scenarios which are outlined in Section 6.

5.3. Model validation and face validity check

The company's economic model was checked for errors by a health economist; however, given this is a CDF review and that the prior model submitted as part of TA557 had already undergone a thorough QC, a further QC using methods from first principles was not conducted on the new models submitted by the company.

Four economic models were submitted as part of this appraisal (as highlighted in Section 4.1), and therefore the ERG did not have sufficient time to QC all model inputs, calculations and results. Generally, the ERG noticed that there were several limitations across the four models (which have arisen since the model submitted alongside CS1 in TA557) which hindered the ability to reliably check the models in a limited time frame. Notably:

- Circular references (i.e. cells that refer to themselves).
- The inclusion of non-relevant comparators and analyses which did not work within the model.

- A number of model error messages (including over 70,000 #REFs in one model submitted).
- The presence of external links.

Despite this, the ERG did cross-check the models and were able to replicate results from IA1 and FA and therefore are able to validate results across models. Whilst the ERG would like to caveat that they cannot say with absolute certainty that no modelling errors have been introduced since the time of the original submission, outside of the limitations acknowledged above, the ERG did not notice any further modelling calculation errors in conducting its review of CS2.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1. Exploratory and sensitivity analyses undertaken by the ERG

This section focuses on the additional analyses used to explore the key areas of uncertainty which have been conducted by the ERG. The analyses are constrained to the population, comparators and trial data provided within the company submission but with adjustments made to model calculations/inputs where necessary. The scenarios are outlined below.

6.1.1. Extended time horizon

The ERG outlined in Section 4.1.4.that the time horizon may not be sufficiently long to be considered a lifetime horizon with a small proportion of people alive at the end of the time horizon. The ERG therefore explores a time horizon of 25 years.

6.1.2. Distributions for OS extrapolation

As noted in Section 4.1.5.1, following guidance produced by the Decision Support Unit (DSU) as part of Technical Support Document (TSD) 14[15] (titled "Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data"), both the log-logistic curves and the generalised gamma curves were considered to be plausible long-term extrapolations of the OS data for both pembrolizumab and SoC. At the time of the original submission the committee also agreed that the generalised gamma may be considered an appropriate fit to the data.[5] This was not provided by the company and therefore has been considered as a scenario by the ERG. The ERG also explored the impact of having a generalised gamma for the pembrolizumab arm and a log-logistic for the SoC arm.

6.1.3. Application of a gradual treatment waning effect applied at 2 years

As outlined within Section 4.1.5.1 within this document, and in Section A.9 of the company submission (refer to CS2 [CDF Review Document A, p.37]), a treatment waning effect was applied to the pembrolizumab combination arm of the economic model. During TA557, both three years and five years were recognised as relevant points at which the treatment effect may start to taper. Typically, where a treatment waning affect is applied, the hazards in the survival curves suddenly switch at a defined time point from the intervention extrapolation to hazards derived from the comparator extrapolation. In reality, however, it is the ERG's understanding that a waning affect can be more gradual over time. Given treatment waning is an area of uncertainty which impacts the ICER, the ERG considered a scenario where treatment waning is

applied from the point of stopping treatment with pembrolizumab (at two years), and occurs gradually until Year 5. This approach assumed a linear transition from the hazards of the pembrolizumab combination therapy curve to the hazards of the SoC curve (over the three years). Further exploratory three to five years. Two-way sensitivity analysis has been conducted applying this adjustment in isolation (using all other settings aligned to the company base case). The results of this analysis are presented in Figure 11. As shown, the lowest ICER is [redacted], relevant when the TWE is applied from five years to 10 years. The highest ICER occurs when the TWE is applied from two years to three years with a corresponding ICER of [redacted]. The ERG application of a gradual TWE between discontinuation and five years corresponded to an ICER of [redacted].

Figure 11: Two-way sensitivity analysis, adjusting treatment waning effect – company preferred base-case

Figure 12 presents results of the economic model when applying the ERG OS curve preferences (generalised gamma for both treatment arms) and varying the TWE start and end time. All other parameters remain set to the company's base case settings. The results of this analysis demonstrated how influential the selection of the OS curve is, as the lowest ICER when using the ERG preferred OS curve is [redacted], occurring when the TWE was applied instantly at three years. The highest ICER occurred when applying the TWE between five and 10 years with a corresponding ICER of [redacted], and the ERG application of a gradual TWE between discontinuation and five years corresponded to an ICER of [redacted].

Figure 12: Two-way sensitivity analysis, adjusting the treatment waning effect - ERG preferred OS

Abbreviations: ERG, Evidence Review Group; OS, overall survival

6.1.4. Generalised gamma parametric distribution for time-on-treatment extrapolation

As noted in Section 4.1.5.3, the ERG had concerns relating to the company's justification in selecting an exponential curve to both the pembrolizumab combination arm and the SoC arm. Following guidance from the DSU in TSD 14,[15] the ERG also considered the generalised gamma a relevant possibility and explored this in scenario analysis. Within the economic model submitted by the company, the generalised gamma was also labelled as the 'base case' survival extrapolation (despite the company submission and base case incorporating the exponential). Therefore, it is possible that the company also considered the generalised gamma a reasonable extrapolation option at some point throughout the model development process.

6.1.5. Utility approach

The ERG explore the use of applying Approach 1 to inform HRQoL within the model (see Section 4.1.64.1.6).

6.1.6. Updated dosing intensity

As outlined in Section 4.1.7, the ERG considered it more appropriate to include dose intensities from the final analysis of KEYNOTE-189.

6.2. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Results from the alternative scenarios undertaken by the ERG are presented in Table 13.

Table 13: Impact of ERG scenario analyses on company ICER

Scenario analyses conducted by the ERG	ICER	+/- ICER £/QALY	Proportional impact in company base case ICER (%)
Company base-case	[redacted]		
Time horizon			
1. 25-year time horizon	[redacted]	*-£930*	[redacted]
Overall survival			
2. Generalised gamma applied to both treatment arms	[redacted]	*+21,789*	[redacted]
3. Generalised gamma applied to the pembrolizumab arm	[redacted]	*+19,929*	[redacted]
Gradual treatment waning affect			

4. Gradual TWE applied between years 2 to 5	[redacted]	*+£3,574*	[redacted]
5. Gradual TWE applied between years 2 to 3	[redacted]	*+£7,479*	[redacted]
6. Gradual TWE applied between years 3 to 5	[redacted]	*+1,733*	[redacted]
7. Gradual TWE applied between years 3 to 10	[redacted]	*-£524*	[redacted]
Time-on-treatment			
8. Generalised gamma parametric distribution for time-on-treatment applied to both treatment arms	[redacted]	*+£916*	[redacted]
Dose intensity			
9. Updated dose intensity from the final analysis of KEYNOTE-189	[redacted]	-£112	[redacted]

Key: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TWE treatment waning effect

6.3. ERG's preferred assumptions

The ERG base case ICER for pembrolizumab combination therapy versus SoC was [redacted] per QALY gained. The following five preferences were adopted:

A. Generalised gamma distributions assigned to both arms for OS

B. Application of a gradual TWE between years 2 to 5

C. Generalised gamma distributions assigned to both arms for ToT

D. Updated dose intensity from KEYNOTE-189 FA

E. Utility method one explored applying utilities based on progression with a TTD decrement applied people with <360 days to live

Figure 13 presents the modelled OS, PFS and ToT using the ERG base case compared to the company base case. As illustrated, the largest difference relates to the approach to modelling OS, where the ERG base case provided slightly lower estimates of survival in applying the TWE combined with the generalised gamma curve. Both approaches show a relatively good fit to the Kaplan-Meier data across PFS, OS and ToT. Results of the ERG preferred assumptions are shown in Table 14.

Figure 13: Comparison of company base case survival versus ERG base case

Key: ERG, Evidence Review Group; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; SoC, standard of care.

Table 14: ERG's preferred model assumptions

A-E	Preferred assumption	Section in ERG report	ICER	+/- ICER incremental in each setting A-E	Cumulative ICER £/QALY
	Company base-case		[redacted]		
A	Scenario 1: Generalised gamma distribution for OS applied to both treatment arms	*5.1.5.1*	[redacted]	£21,789	[redacted]
A+B	Scenario 4: Gradual TWE applied between years 2 to 5	*5.1.5.1*	[redacted]	-£4,024	[redacted]
A+B+C	Scenario 8: Generalised gamma parametric distribution for time-on-treatment applied to both treatment arms	*5.1.5.3*	[redacted]	£1,295	[redacted]
A+B+C +D	Scenario 9: Updated dose intensity from KEYNOTE-189	*5.1.7*	[redacted]	-£163	[redacted]

A+B+C +D+E	Company scenario 5: Utility method 1 applied	*5.1.6*	[redacted]	£3,593	[redacted]

Key: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

A breakdown of the ERG deterministic base case is provided in Table 15. Results indicated that that pembrolizumab combination therapy was estimated to provide an additional [redacted] QALYs at an incremental cost of [redacted].

Table 15: ERG base case results (deterministic)

	Costs	QALYs	∆Cost	∆QALY	ICER
Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

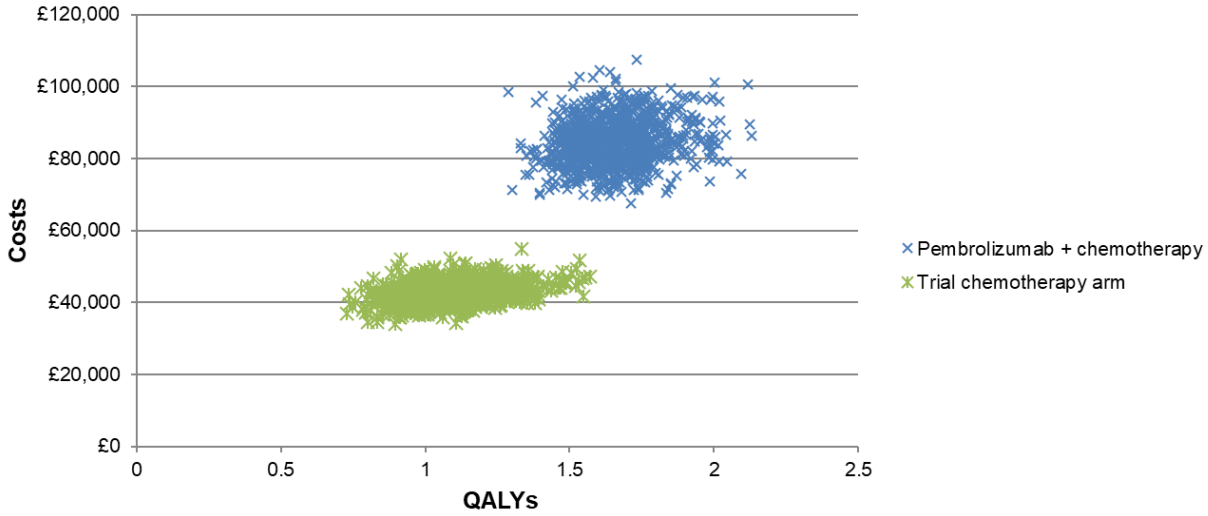
PSA results are presented in Figure 14 and Figure 15. The results of the PSA (Table 16) are similar to the deterministic analysis with pembrolizumab combination therapy predicted to provide an additional [redacted] QALYs and an incremental cost of [redacted]. At a willingness to pay threshold of £50,000 per QALY, there is a 4.3% probability that pembrolizumab is cost-effective (in comparison to 16.2% presented in the company probabilistic base case).

Table 16: ERG base case results (probabilistic)

	Costs	QALYs	∆Cost	∆QALY	ICER
Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

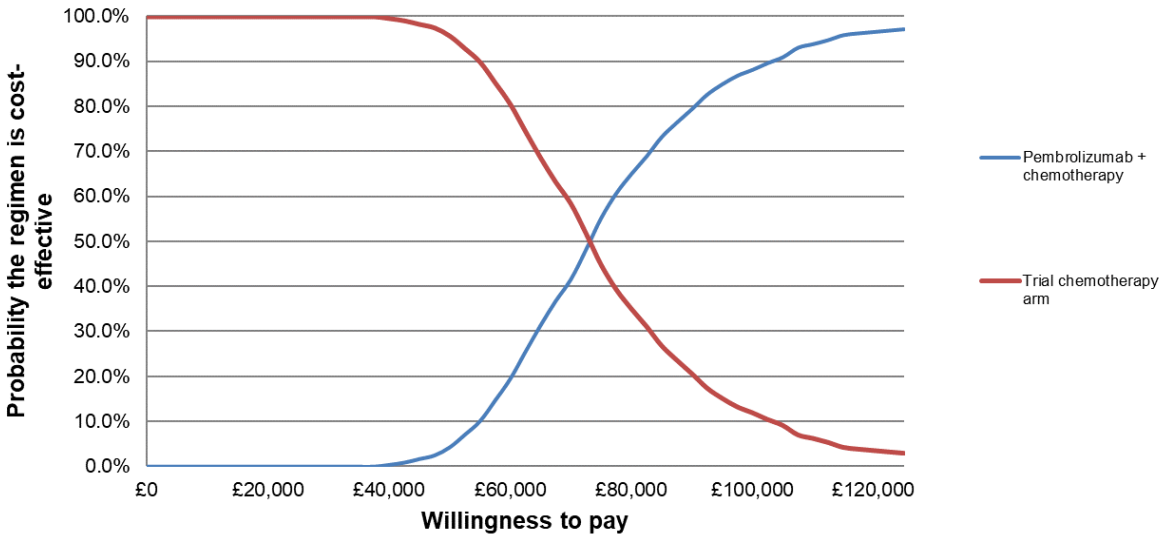
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Figure 14: Cost-effectiveness plane – ERG base case



Abbreviations: ERG, Evidence Review Group; QALY, quality adjusted life year

Figure 15: Cost-effectiveness acceptability curve – ERG base case



Abbreviations: ERG, Evidence Review Group; QALY, quality adjusted life year

6.4. Conclusions of the cost-effectiveness section

- The company has submitted a revised cost-effectiveness analysis based on the original model submitted in TA557. The model submitted alongside this appraisal ID1584 follows the same model structure, with the main differences being:
  - The use of additional follow up data from the KEYNOTE-189 trial (referred to as the final analysis).

  - The approach to utilities is slightly different to the base case at the time of the original appraisal.
  - The selection of the parametric survival models for OS, PFS and ToT.

- Otherwise approaches, underlying model assumptions, and estimates remained largely the same. The company's submission is therefore sufficiently aligned with the scope of this appraisal.
- The final analysis reinforces the IA1 data seen in TA557 indicating that pembrolizumab combination therapy is likely to offer a survival benefit (both progression-free survival and overall survival) in comparison to SoC which is chemotherapy.
- There is still uncertainty within the economic model, and the ICER is greatly influenced by the choice of OS extrapolation selected. In TA557 the committee considered the log-logistic and the generalised gamma to be plausible models to consider for decision making. The ERG believes that the same is true with the FA model and that both the log-logistic and generalised gamma are equally plausible extrapolations of the OS data (for both arms).
- The method used to incorporate HRQoL also influences the ICER and should be given careful consideration.
- The company base case ICER with the PAS [redacted] applied was [redacted].
- Scenario analysis explored by the company and the ERG consistently show that the ICER varies between [redacted] and [redacted] with most scenarios being greater than £50,000 per incremental QALY gained.

7. END OF LIFE

Within CS1,[4] the company put forward a case that, for the population under consideration, pembrolizumab met NICE's end-of-life criteria. Evidence from the company and ERG models suggested that the average OS for SOC was under the 24 months and the extension to life achieved with pembrolizumab exceeded the three-months. Despite the clinical uncertainty associated with pembrolizumab in this population, there was agreement amongst the committee that the population fulfills the criteria for end-of-life status.

Within the subgroup analysis (for people with PD-L1+ disease whose tumours express ≥50% TPS), the committee concluded that NICE's end-of-life criteria was not satisfied. This was because:

- Modelled mean OS for the pembrolizumab monotherapy was 28 months
- The ITC showed no statistically significant difference in OS between pembrolizumab combination and pembrolizumab monotherapy.

Within the updated CS, the company results indicated that, the undiscounted life years were 2.00 for the standard of care arm; survival was predicted to be exactly 24 months – the cut-off for the end-of-life criteria. Despite this, the other five extrapolated curves indicated a mean survival of <24 months for the SoC arm, and in all extrapolations the pembrolizumab combination offered a survival benefit of >3 months (as shown below in

Figure 16).

Figure 16: Survival benefit of pembrolizumab across all OS extrapolations for pembrolizumab combination versus SoC

Key: OS, overall survival; Pembro, pembrolizumab combination therapy; SoC, standard of care;

Notes(s): The red-dashed line represents a threshold of 3 months of additional survival (as outlined in the end-of-life criteria)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small cell lung cancer [Cancer Drugs Fund Review of TA557]

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it 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 appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission, the terms of engagement for the CDF review (ToE) and the original appraisal (TA557)
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

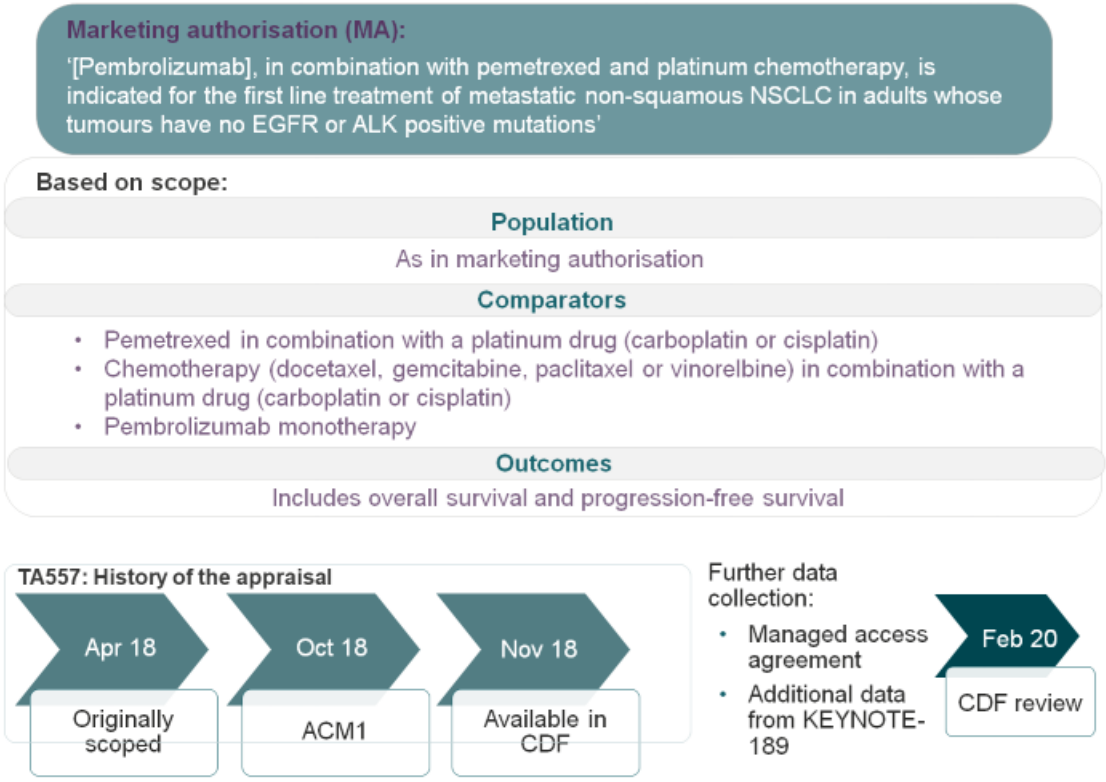
- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts
- the evidence review group (ERG) report
- the committee discussion in the original appraisal (TA557)
- the terms of engagement for the CDF review

Issue date: March 2020

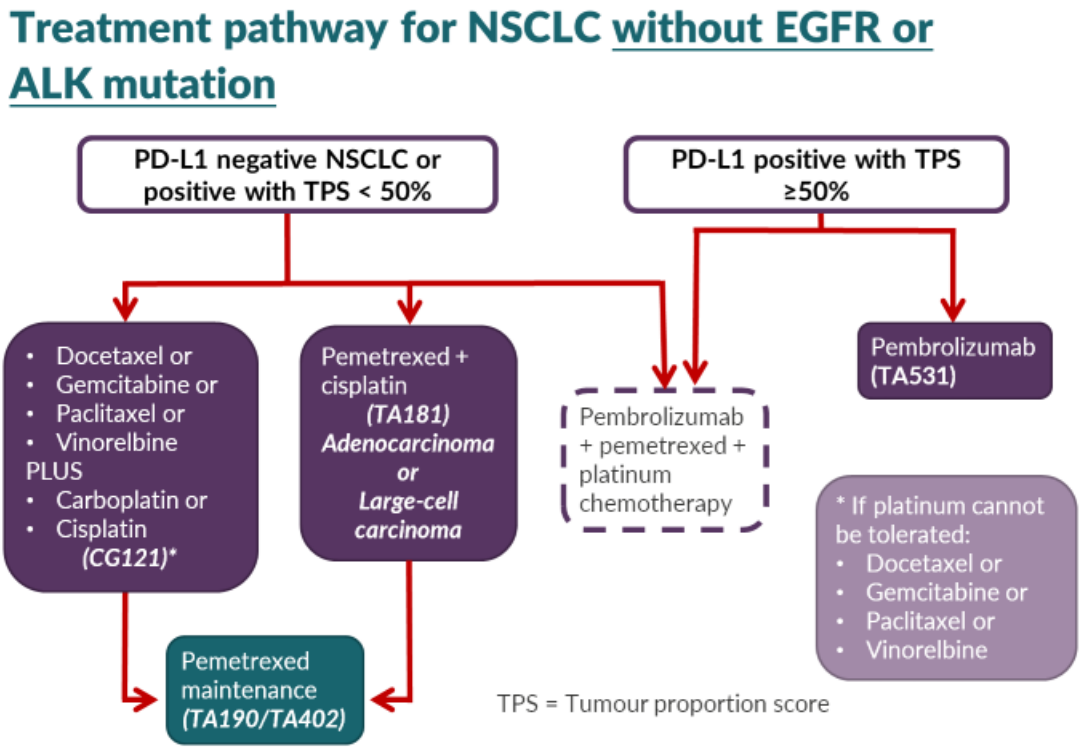
The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Appraisal background



1.2 Treatment pathway



1.3 Key considerations from original appraisal

Committee preference from original appraisal	Did company follow/address this in CDF review?
Adults with untreated, metastatic, non-squamous NSCLC lacking EGFR- and/or ALK-positive mutation	✔
Network meta-analysis to compare pembrolizumab combination with 'other chemotherapy' treatments used in NHS practice	✔ (Results for the comparison were not presented in this submission but company provided a rationale for not doing so)
ITC to compare pembrolizumab combination with pembrolizumab monotherapy for people whose tumours express PD-L1 with ≥50% TPS	✔

Plausible OS curves - the log-logistic and generalized gamma	✗ (Log-logistic only – based on new data)
An adjustment for background mortality should be included	✗ (But rationale provided)
A progression-based approach to calculate utilities	✗
Preference to cap the benefit of pembrolizumab at 3 years and 5 years from the start of treatment	✔
End of life	Criteria still met for PD-L1 <50% only Criteria still not met for PD-L1 >50%

1.4 Clinical trial – KEYNOTE-189

Additional [redacted] months of data collection in trial (cut-off [redacted]) compared to last data seen by committee

KEYNOTE-189	Phase III RCT, n = 616
Population	Adults with advanced or metastatic non-squamous NSCLC; no EGFR or ALK; ECOG ≤1
Intervention	Pembrolizumab (200mg) plus pemetrexed (500mg) and a platinum-based chemotherapy The recommended dose of pembrolizumab as part of combination therapy is 200 mg every 3 weeks administered as an intravenous infusion over 30 minutes
Comparator	Saline placebo plus pemetrexed (500mg) and a platinum-based chemotherapy
Primary outcome	OS and PFS
Key subgroups	Patients with PD-L1+ tumour proportion score (TPS) ≥50%

Key abbreviations in appraisal

AEs, adverse events; ALK, anaplastic lymphoma kinase; AUC, area under the curve; CT, chemotherapy; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression free survival

1.5 Updated clinical trial results – overall survival

		Updated results from KEYNOTE-189 (cut-off [redacted], database lock [redacted])			Results from KEYNOTE-189 presented in first appraisal committee meeting of TA557		
Treatment	N	Median OS (months) (95% CI)	Treatment vs. Control		Median OS (months) (95% CI)	Treatment vs. Control	
			Hazard ratio (95% CI)	p-value		Hazard ratio (95% CI)	p-value
Control	206	[redacted]	---	---	11.3 (8.7, 15.1)	---	---
Pembrolizumab combination	410	[redacted]	[redacted]	[redacted]	Not reached	0.49 (0.38, 0.64)	0.00001

CI: confidence interval

1.6 Updated clinical trial results – progression-free survival

		Updated results from KEYNOTE-189 (cut-off [redacted], database lock [redacted])			Results from KEYNOTE-189 presented in first appraisal committee meeting of TA557		
Treatment	N	Median PFS (months)	Treatment vs. Control		Median PFS (months) (95% CI)	Treatment vs. Control	
			Hazard ratio (95% CI)	p-value		Hazard ratio (95% CI)	p-value
Control	206	[redacted]	---	---	4.9 (4.7, 5.5)	---	---
Pembrolizumab combination	410	[redacted]	[redacted]	[redacted]	8.8 (7.6, 9.2)	0.52 (0.43, 0.64)	0.0001

CI: confidence interval

2. Remaining issues after data collection in CDF period, to be addressed in this review

#	Issue	Matches ToE?	Why this is being explored in CDF review	Technical team consideration
1	Comparative evidence	No	It is important to make the most realistic comparison between pembrolizumab combination and the standard of care in NHS clinical practice.	New evidence could change the conclusion of the NMA and comparisons with the most appropriate alternative treatments could impact the base case ICER.
2	PD-L1 expression subgroup	No	Further data from KEYNOTE-189 could reduce uncertainty in OS and PFS estimates according to expression of PD-L1.	It is relevant to reconsider subgroups considering the updated clinical data.
3	OS extrapolation	No	ERG and committee identified multiple plausible approaches.	Committee may wish to consider the different plausible extrapolation distributions.
4	ToT extrapolation	No	Company and ERG used different approaches.	Committee may wish to consider the different plausible extrapolation distributions.
5	Time horizon	N/A	Higher proportion of people alive after 20-years following company's updated model.	A 25-year time horizon is preferable to ensure all important differences in cost or QALYs between technologies are captured in the model.
6	Treatment effect duration	Yes	Company and ERG use different approaches.	Committee may wish to consider the 3-year, 5-year, and ERG's 2-year scenarios to determine consistency with other NICE appraisals.
7	Utilities	No	Company deviated from the committee's preferred approach.	The technical team considers the committee's approach as concluded in TA557 to be maintained.

3. Summary of the draft technical report

3.1 In summary, the technical team considered the following:

Issue 1 The committee's conclusion from TA557 that pembrolizumab combination would be considered as an alternative to other chemotherapy is maintained.

Issue 2 The committee may wish to consider if PD-L1 sub-group results are appropriate and reliable for decision-making considering updated data.

Issue 3 The generalised gamma model should be applied to both treatment arms to extrapolate overall survival data.

Issue 4 The generalised gamma model should be applied to both treatment arms to extrapolate time-on-treatment data.

Issue 5 The time horizon should be increased to 25 years.

Issue 6 3-year treatment effect (2+1, which represents 2 years of treatment and 1 year of follow-up) appears most plausible, but committee may wish to consider 5-year effect also, as well as the conservative 2-year scenario analysis.

Issue 7 The committee's preference from TA557 is maintained with progression based utilities with a decrement applied in the last year of life.

3.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The clinical trial evidence is immature with a high level of uncertainty in long-term survival outcomes for this indication.

3.3 The cost-effectiveness results include a commercial arrangement (patient access scheme) for pembrolizumab.

3.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of

[redacted] per QALY gained (see table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate).

3.5 It was decided in TA557 that the end-of-life criteria were met for pembrolizumab combination compared with chemotherapy but not met for the comparison with pembrolizumab monotherapy (see TA557 FAD sections 3.17 and 3.18).

3.6 The technology is not considered innovative (see Table 3: Other issues for information).

3.7 No equality issues were identified (see Table 3: Other issues for information).

4. Key issues for consideration

Issue 1 – Comparison with other chemotherapy

Questions for engagement	1. Is the company's approach to comparing pembrolizumab combination with other chemotherapy treatments representative of clinical practice?
Background/description of issue	**TA557:** The original scope (TA557), had included other chemotherapy treatments as a comparator (docetaxel, gemcitabine, paclitaxel or vinorelbine as monotherapy with carboplatin or cisplatin, with or without pemetrexed therapy). The company's original submission included a network meta-analysis (NMA) comparing pembrolizumab combination therapy with other chemotherapy which indicated no significant difference between the platinum doublet chemotherapy interventions commonly used in UK clinical practice. The ERG recognised clinical feedback that some of the other chemotherapy treatments were not commonly used in UK clinical practice. The committee concluded that although the use of other chemotherapy in clinical practice is limited, pembrolizumab combination would be considered as an alternative to these treatments. **CDF review:** The company did not present a comparison of pembrolizumab combination with other chemotherapy treatments ((docetaxel, gemcitabine, paclitaxel or vinorelbine as monotherapy), with carboplatin or cisplatin, with or without pemetrexed maintenance therapy) by means of an NMA or an updated systematic literature review (SLR). **The company's** justification was that results from the NMA conducted in the original appraisal showed no statistically significant difference between the specified platinum doublet chemotherapy interventions. The company referenced expert clinical advice given in TA557 that platinum doublet chemotherapy interventions were not commonly used in UK clinical practice. The company further argued that in the appraisal of atezolizumab (TA520), pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was considered the relevant comparator for the first-line non-squamous NSCLC population by the CDF clinical lead.

	The ERG was broadly satisfied with the methods of the NMA that was presented in the original appraisal. While the ERG accepted the company's rationale for not including other chemotherapy, it also noted that the degree to which new evidence would have changed the conclusions of the NMA was unclear.
Why this issue is important	It is important to make the most realistic comparison between pembrolizumab combination and the standard of care in NHS clinical practice.
Technical team preliminary judgement and rationale	The committee's conclusion from TA557 that pembrolizumab combination would be considered as an alternative to other chemotherapy is maintained. New evidence could change the conclusion of the NMA and comparisons with the most appropriate alternative treatments could impact the base case ICER.

Issue 2 – Comparison with pembrolizumab monotherapy

Questions for engagement	2. Is the additional data used to update the indirect treatment comparison (ITC) enough to reduce the uncertainty in the overall survival estimates for pembrolizumab combination therapy compared with pembrolizumab monotherapy? 3. Is it still the case that pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% TPS does not meet NICE's end-of-life criteria?
Background/description of issue	**TA557:** In the original appraisal, the company used an ITC to compare pembrolizumab combination with pembrolizumab monotherapy for people whose tumours express PD-L1 with ≥50% TPS. The ITC found a large effect and 95% credible intervals around the effect were very wide. The difference was not statistically significant and the company did not include data from a relevant trial (KEYNOTE-021G). Although the committee agreed it would not have a substantial effect on the final estimate, further data from KEYNOTE-189 could help to reduce the uncertainty in the OS estimates. The committee concluded that pembrolizumab combination would be considered as an alternative to pembrolizumab monotherapy only in PD-L1-positive NSCLC if the tumour expresses at least a 50% tumour proportion score. The committee noted that because of the uncertainty of the indirect treatment comparison results which informed this analysis, it was not clear if life expectancy is less than 24 months for this population. The committee concluded that pembrolizumab combination compared with pembrolizumab monotherapy in people whose tumours express a tumour proportion score of at least 50% did not meet the end-of-life criteria. **CDF review:** **The company** provided an updated ITC of pembrolizumab combination vs pembrolizumab monotherapy and results were presented for the PD-L1+ TPS ≥50% in their clarification response. **The ERG** considered the company's methods for the ITC to be broadly appropriate. At variance with the analysis presented in TA557, four trials (KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, KEYNOTE-021G) were used, thus integrating all available trial evidence. Results suggested a numerical improvement in OS (HR=[redacted]) and a potential benefit in PFS (HR=[redacted]); however, the latter should be interpreted with caution as tests for

	proportional hazards assumptions were not presented and visual inspection of curves suggested these assumptions were untenable.
Why this issue is important	Further analyses of the data from KEYNOTE-189 could help to reduce the uncertainty in the overall survival estimates for pembrolizumab combination therapy compared with pembrolizumab monotherapy for the PD-L1+ TPS ≥50% population. This could reduce the uncertainty and determine whether pembrolizumab combination compared with pembrolizumab monotherapy in people whose tumours express a tumour proportion score of at least 50% meet the end-of-life criteria.
Technical team preliminary judgement and rationale	The committee's conclusion from TA557 that pembrolizumab combination would be considered as an alternative to pembrolizumab monotherapy for the for the PD-L1+ TPS ≥50% population is maintained. Pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% TPS does not meet NICE's end-of-life criteria and that the resulting ICER of [redacted] is above the range normally considered cost-effective.

Issue 3 – Extrapolation of overall survival

Questions for engagement	4. Is the log-logistic distribution or the generalised gamma distribution the most appropriate extrapolation of OS, for both the pembrolizumab combination and standard of care arms?
Background/description of issue	**TA557:** To extrapolate overall survival for pembrolizumab combination compared with standard care in the intention-to-treat population, a 2-phase piecewise model with an exponential distribution at a 28-week cut-off was chosen by the company. The ERG did not consider that this approach was appropriate and instead preferred a fully-fitted parameterised curve using the log-logistic distribution from week 0. The committee concluded that various plausible curves can be fitted to the Kaplan–Meier data including the log-logistic and generalised gamma curves applied independently to both arms.

	CDF review: **The company** explored log-logistic extrapolation but did not explore generalised gamma curves to model OS in their base case or as a scenario. The company stated a preference for a log-logistic model based on inspection of its visual fit to the Kaplan-Meier curves and interpretation of statistical goodness-of-fit scores (i.e. Akaike's and Bayesian Information Criteria [AIC and BIC]). The company noted that the ERG previously stated a preference for the log-logistic model over a piecewise approach using the Kaplan-Meier curve followed by an exponential model (at Week-28). In their clarification response, the company also noted that *"Following the recommendation from the DSU, the same functional form was selected for the separate parametric models according to that fitting most closely the data overall"*. This approach led to a 5-year survival estimate of 8.7% which is within the expected range for the SoC arm (5-11%, as discussed in the TA557 FAD). **The ERG** noted that the log-logistic model was not the statistically best fitting model and highlighted the importance of considering alternative models for OS. The ERG considered both the log-logistic and generalised gamma parameterisations suitable candidates to inform the cost-effectiveness analysis. The ERG compared these models which shows that the extrapolations for the SoC arm are similar using either functional form, yet for the pembrolizumab combination arm the extrapolations differ markedly (e.g. five-year survival is 19.8% for the log-logistic model, versus 12.1% for the generalised gamma model). Both of these models yield estimates of five-year OS that exceed the expected range for the SoC arm (5-11%, as discussed in the TA557 FAD). The ERG concluded that the generalised gamma provides a better statistical fit to the KEYNOTE-189 trial data, as well as plausible long-term extrapolation. Accordingly, the ERG opted to select the generalised gamma models for both treatment arms to inform its base case OS projections.
Why this issue is important	The choice of distribution has a large impact on the ICER. Using the generalised gamma model applied to both treatment arms, the ICER increases from [redacted] in the company base case to [redacted].
Technical team preliminary judgement and rationale	It is appropriate to use the Kaplan-Meier curve with the tail extrapolated using the generalised gamma rather than the log logistic distribution, because it results in more clinically plausible estimates of overall survival at year 5 for patients in both arms of the clinical trial.

Issue 4 – Extrapolation of time-on-treatment

Questions for engagement	5. Is the exponential distribution or the generalised gamma distribution the most appropriate extrapolation of time-on-treatment, for both the pembrolizumab combination and standard of care arms?
Background/description of issue	**TA557:** In the original appraisal, the company used an exponential model for the pembrolizumab combination arm, and a Weibull model for the SoC arm for the extrapolation of time-on-treatment (ToT). The committee stated no preference, so it was assumed that the company's original model for ToT was suitable. **CDF review:** **The company** found that both the exponential and the generalised gamma had the best statistical fit for both treatment arms (using AIC/BIC statistics and visual inspection). For consistency with the submission at the CDF entry point, the company therefore decided upon use of the exponential for the extrapolation of ToT for both arms in their updated model. **The ERG** considered the exponential models to provide a reasonable fit to the Kaplan-Meier curves for both arms, but they highlighted some important considerations: • the model for pembrolizumab combination slightly under-estimates the Kaplan-Meier curve between one and two years, yet this is a feature of the majority of the models fitted by the company • it was unclear to the ERG why the rate of discontinuation could be assumed constant, when considering a combination of three components, one of which is assumed to be withdrawn at exactly two years. The ERG noted that by using an exponential model, the company assumed proportional hazards between the two arms for this outcome (given that the exponential model considers a constant hazard over time). The ERG considered it was inappropriate to assume constant hazards for ToT and that no evidence was provided by the company to support the proportional hazards assumption. The statistical goodness-of-fit scores for ToT, demonstrated that the generalised gamma was the

	best fitting model based on AIC, and exponential based on BIC. The same relationship was seen in the models fit to the SoC arm. The ERG's preference was to select a generalised gamma curve for both treatment arms to inform their base case.
Why this issue is important	The choice of distribution has a small impact on the ICER. Using the generalised gamma model applied to both treatment arms, the ICER increases from [redacted] in the company base case to [redacted].
Technical team preliminary judgement and rationale	For the extrapolation of ToT, it is appropriate to use a generalised gamma curve for both treatment arms.

Issue 5 – Time horizon

Questions for engagement	6. Are all differences in costs and effects attributable to pembrolizumab combination likely to be captured in a 20-year time horizon?
Background/description of issue	**TA557:** In the original appraisal, the company noted that a 20-year time horizon was appropriate as 0% of people in the pembrolizumab combination arm and 0% in the SoC arm were still alive after that period. The committee and the ERG considered this appropriate and no further alternative scenarios were explored in relation to the model time horizon. **CDF review:** **The company's** approach to the time horizon remains unchanged from the original appraisal, using a 20-year (effectively life-time) time horizon. **The ERG** noted that within the company's revised economic model, after 20 years, 3% people in the pembrolizumab arm and 1.3% in the chemotherapy arm are alive after this period. Given these higher proportions, the ERG considered that either the time-horizon is not sufficiently long enough to capture all relevant treatment effects (as outlined in the NICE methods guidance) or alternatively

	that the OS extrapolations considered within the company base case may be too optimistic. The ERG provided a scenario to explore an increase to the time horizon to 25-years.
Why this issue is important	The duration of the time horizon has an impact on the cost-effectiveness results as differences in costs and outcomes continue beyond 20 years. The ERG's scenario analysis when using a 25-year time horizon reduces the ICER to [redacted] from the company's base-case of [redacted].
Technical team preliminary judgement and rationale	A 25-year time horizon is preferable to ensure all important differences in cost or QALYs between technologies are captured in the model.

Issue 6 – Treatment effect duration

Questions for engagement	7. Is a 2-year, 3-year or 5-year duration of treatment effect for pembrolizumab appropriate? 8. Is there any additional evidence which could be used to inform the duration of treatment effect for pembrolizumab in this indication?
Background/description of issue	**TA557:** In the original appraisal, the company stated that its model included a 2-year treatment stopping rule and a life-time treatment effect. The committee concluded that a 2-year stopping rule was consistent with NICE's technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer and was acceptable. The committee also considered that the duration of treatment effect was an area of uncertainty for new immunotherapies and was aware that in previous technology appraisals in this disease area, scenarios of a treatment effect lasting between 3 and 5 years (after starting treatment) had been considered. **CDF review:** **The company** applied a treatment waning effect (TWE) to the pembrolizumab combination arm of the economic model. A 5-year cap from the start of treatment was implemented on the treatment

	duration, as a base case. A 3-year and 10-year cap, as well as a lifetime treatment effect, were presented as scenario analyses. Company's analysis – adjusting the TWE:  **The ERG** noted that using the company's model setting, the estimated hazard of death for patients on the pembrolizumab combination arm is assumed to be equal to the SoC arm after five years. If the TWE is disabled in the base case analysis, the ICER decreases from [redacted] to [redacted]. However, should generalised gamma models be applied for both arms, removal of the TWE causes the ICER to increase from [redacted] to [redacted]. Using a combination of a generalised gamma model for the pembrolizumab combination arm, and a log-logistic model for the SoC arm, the ICER is [redacted] with the TWE, and [redacted] without the TWE. These results, which appear to lack face validity when the generalised gamma curve is selected for pembrolizumab, is a direct result of the extrapolated curves which produce a lower hazard at five years for the SoC arm than the pembrolizumab arm. Hence, applying a TWE increases survival for pembrolizumab. Given there is uncertainty in the timepoint at which a TWE should be applied, and treatment with pembrolizumab stops at two years, the ERG implemented a new scenario which applied a TWE gradually from the point of discontinuation up until the upper bound outlined in TA557 (five-years). This gradual effect happens linearly with a weighted hazard being produced at each cycle, to generate an adjusted pembrolizumab combination OS estimate. Further ERG analyses were also explored which apply the gradual approach until 10 years (the upper bound provided in company scenario analysis). Applying a gradual TWE approach avoids a sudden change in hazards that may

	sometimes be seen with applying a TWE to extrapolations of immuno-oncologies versus chemotherapy. The ERG base case approach assumed a generalised gamma for both treatment arms and applied a gradual TWE between two and five years. ERG's analysis – adjusting the TWE*:  *applying the ERG OS curve preferences (generalised gamma for both treatment arms) and varying the TWE start and end time. All other parameters remain set to the company's base case settings.
Why this issue is important	The ongoing treatment effect influences the QALYs and thus the ICER. Treatment waning is an area of uncertainty which can have a large impact on the ICER.
Technical team preliminary judgement and rationale	The technical team considers that there is uncertainty about the duration of pembrolizumab's relative treatment effect. The committee considered both 3-year and 5-year durations to be plausible in the original appraisal and there is no new clinical evidence to justify any change to this conclusion.

Issue 7 – Health-related quality of life

Questions for engagement	9. What is the most appropriate approach to incorporate both progression status and time-to-death within the estimation of utilities?
Background/description of issue	**TA557:** In the original appraisal, the committee discussed the company's time-to-death approach to estimate utility values using EQ-5D data from KEYNOTE-189. Utility values for pembrolizumab combination and standard care were pooled and divided into 4 groups based on time to death (from less than 30 days to at least 360 days). As part of TA557 two methods were explored which incorporated both progression status and time-to-death within the estimation of utilities: 1. Progression based utilities with a decrement applied in the last year of life (Approach 1) 2. Time-to-death utilities with a decrement applied to account for progression (Approach 2) The committee preference at the time of TA557 was a combined approach (Approach 1) to estimating utility values to fully capture the quality-of-life changes for people with NSCLC. **CDF review:** **The company's** base case incorporated utilities based on time-to-death with an additional decrement applied for progression. The company outlined that this was based on clinical expert opinion received throughout TA557, and the committee preferences at the point of CDF entry. **The ERG** noted that the company's approach to utilities had changed since the original appraisal. The ERG highlighted that the utility decrement from either approach was not varied in the company's sensitivity analysis, meaning that the underlying uncertainty was likely to be underestimated in the sensitivity analyses provided by the company. Further to this, the utilities included within the analysis are varied independently and do not apply a multi-variate distribution. This means that within the one-way sensitivity analysis or the probabilistic sensitivity analysis it is

	possible that the parameter values selected will lack face validity. The ERG acknowledged that both approaches have limitations. Notably, the merging of the approaches may double count the effects of progression or being close to death. Secondly, that neither approach has been updated using the KEYNOTE-189 final analysis data. The ERG applied the committee's preferred assumption from TA557 and used a progression based approach applying a decrement for patients who are likely to live less than 360 days.
Why this issue is important	The economic model is sensitive to the approach incorporated and incorporating Approach 1 increases the base case ICER by [redacted].
Technical team preliminary judgement and rationale	The technical team considers the committee's preference for progression based utilities with a decrement applied in the last year of life (approach 1) to remain the same.

5. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate (deterministic base case for pembrolizumab with pemetrexed and platinum chemotherapy compared to placebo with pemetrexed and carboplatin or cisplatin

Alteration	Technical team rationale	ICER	Change from base case
Company base case	Deterministic ICER	[redacted]	–
1. Time horizon 25-years	Issue 5	[redacted]	[redacted]
2. OS extrapolated using generalised gamma applied to both treatment arms	Issue 3	[redacted]	[redacted]
3. TWE applied between years 3 to 5	Issue 6	[redacted]	[redacted]
4. ToT extrapolated using generalised gamma applied to both treatment arms	Issue 4	[redacted]	[redacted]
5. Updated dose intensity from the final analysis of KEYNOTE-189	See table 3	[redacted]	[redacted]
6. Progression based utilities with a decrement applied in the last year of life	Issue 7	[redacted]	[redacted]
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	–	[redacted]	[redacted]

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Immature evidence base	Despite the additional KEYNOTE-189 data, there is still a high level of uncertainty in long-term survival outcomes for this indication, both for pembrolizumab and immunotherapies in general. The analyses are based on extrapolated mean values.	Lack of long-term data increases uncertainty in the decision.

Table 3: Other issues for information

<table>
<tr><th>Issue</th><th>Comments</th></tr>
<tr><td>Stopping rule</td><td>The technology is subject to a 2-year stopping rule in this indication, as outlined in the recommendation in the original appraisal (TA557).</td></tr>
<tr><td>Implementation of company model</td><td>There were no changes to the model structure, population, intervention, perspective, time horizon or discounting in the model submitted by the company, which was accepted previously by the committee. The company followed the committee's preferred assumptions in the ToE, but made two main deviations:
The approach to utilities, which is slightly different to the base case approach used at the time of the original appraisal (see Issue 7).
The selection of the parametric survival models for OS, PFS and ToT (see Issues 3 and 4).
In its critique, the ERG found some minor errors in the model, which the company corrected as part of their response to clarification. These changes did not affect the ICER. Both the ERG's report and the technical report were based on the corrected model.</td></tr>
<tr><td>Dose</td><td>To inform drug costs, dosing intensity was taken from the KEYNOTE-189 trial. At clarification stage the company provided the ERG with updated dose intensity from the final analysis. Overall, although there was little difference, the ERG considered it more appropriate to incorporate the updated dose intensities. These values have therefore been incorporated into the ERG base case. Aside from this, all costs are aligned to the original company submission used to inform TA557.
<table>
<tr><th></th><th colspan="2">Dosing intensity</th></tr>
<tr><th>Trial data-cut</th><th>Pembrolizumab</th><th>SoC</th></tr>
<tr><td>KEYNOTE-189 interim analysis</td><td>95.6%</td><td>96.4%</td></tr>
<tr><td>KEYNOTE-189 final analysis</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td></tr>
</table>

Issue	Comments
PFS	The company provided a piecewise approach wherein the Kaplan-Meier curve is followed up until Week 21, followed by a Weibull model. In the updated model, progression status informs utility values, and thus this approach impacts cost-effectiveness results. At clarification stage, the company provided additional evidence concerning the rationale for using a piecewise approach. The ERG would have preferred to explore the option of using a fully parametric approach to model PFS as well as the piecewise approach adopted by the company. In spite of the concerns raised by the ERG above, the base-case projections (KM + Weibull) provided by the company appear to provide a reasonable fit to the Kaplan-Meier curves, and are therefore considered a suitable basis for informing decision making, alongside the models that consider alternative cut points.
End-of-life	In TA557, evidence from the company and ERG models suggested that the average OS for SoC was under the 24 months and the extension to life achieved with pembrolizumab exceeded the three-months. This was for a population whose tumours express a tumour proportion score of less than 50% and were treated with pembrolizumab combination compared with chemotherapy. Despite the clinical uncertainty associated with pembrolizumab in this population, there was agreement amongst the committee that the population fulfils the criteria for end-of-life status. Within the subgroup analysis (pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% tumour proportion score), the committee concluded that NICE's end-of-life criteria was not satisfied. This was because: • Modelled mean OS for the pembrolizumab monotherapy was 28 months. • The ITC showed no statistically significant difference in OS between pembrolizumab combination and pembrolizumab monotherapy.
Innovation	The technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	No equality issues were identified in the original appraisal. No new issues have been raised in this CDF review process

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Technical engagement response form

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (CDF Review of TA557) [ID1584]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical 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 questions below. You do not have to answer every question. 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 summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm on 18 March 2020**

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 technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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)	**MSD**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Comparison with other chemotherapy	
Is the company's approach to comparing pembrolizumab combination with other chemotherapy treatments representative of clinical practice?	As detailed in the company submission (ref), it was agreed by NICE and ERG at the kick off meeting, that it was not relevant nor necessary to present an updated NMA. This decision was made in light of the NMA results presented in the original submission which indicated no significant difference between the platinum doublet chemotherapy interventions commonly used in UK clinical practice. In addition, the results of the NMA were supported by clinical expert advice elicited during TA557. Furthermore, the CDF clinical lead stated during the appraisal of TA520 (ref) that, pemetrexed plus platinum, the regimen used as the comparator in the KEYNOTE-189 clinical trial is the relevant comparator for the patient population covered in the indication under discussion. Clinical expert opinion elicited by MSD during the current appraisal confirms that the platinum doublet chemotherapy regimens, included in the NMA presented at the pointed of CDF entry are still considered of equal efficacy and that clinical practice has not changed since the submission at the point of CDF entry. This insight was echoed during the technical engagement call of this current appraisal, where the clinical expert on the call described there had been no change in the backbone chemotherapy and the regimen used in 1L non-squamous NSCLC. The clinical expert also added that platinum and pemetrexed, the comparator in the pivotal trial is the most relevant regimen. Clinical expert opinion elicited by MSD, validated that there have been no significant publications, regarded of high importance, disseminated within the clinical community which would result in a change in the assumption that the comparator within the pivotal is considered the most relevant. Therefore it should be accepted that, since the chemotherapies are still considered of equal efficacy and the trial comparator is the relevant comparator for this patient population, the comparison in the KEYNOTE-189 trial is the most relevant and realistic comparison for NHS clinical practice.

MSD are not aware of any studies, relevant to TA557, which would imply different conclusions to the NMA for platinum doublets in metastatic non-squamous NSCLC. The SLR was carried forward to a search date of October 2019, under the same methodology as the SLR presented in the submission at the point of CDF entry. In all, no publications associated with trials relevant to the KN189 UK submission, aside from several abstracts associated with KEYNOTE-189 and KEYNOTE-021G, were identified. The findings are listed below. Of note, none of the below studies would provide indirect evidence between pembrolizumab-containing regimens and platinum doublet chemotherapy in the UK networks.

Study with publication identified between April 2018 and October 2019	Reason not relevant to KN189 UK submission
CheckMate227	Intervention (Nivolumab)
CLEAR	Intervention (bevacizumab-containing regimens)
IMpower110	Intervention (Atezolizumab)
IMpower110	Intervention (Atezolizumab)
IMpower130	Intervention (Atezolizumab)
IMpower130	Intervention (Atezolizumab)
IMpower131	Intervention (Atezolizumab)
IMpower132	Intervention (Atezolizumab)
IMpower150	Intervention (Atezolizumab)
KEYNOTE-021G	--
KEYNOTE-024	PD-L1 selected trial
KEYNOTE-042	PD-L1 selected trial
KEYNOTE-189	--
KEYNOTE-407	Population (squamous histology)
MYSTIC	Intervention (durvalumab)
NAVOtrial03	Population (squamous histology)
Petty 2019	ECOG PS >=2
Watanabe 2019	Population (squamous histology)

	The KEYNOTE-189 FA data are not yet published, therefore currently there haven't been any publications using the data presented in this current submission.Therefore, as concluded on the technical engagement call MSD think it is reasonable to assume, based on the above rationale and the feedback during the technical engagement call, that this issue can be considered resolved.
Issue 2: Comparison with pembrolizumab monotherapy	
Is the additional data used to update the indirect treatment comparison (ITC) enough to reduce the uncertainty in the overall survival estimates for pembrolizumab combination therapy compared with pembrolizumab monotherapy?	As highlighted in the technical report, the updated ITC incorporated all available trial evidence, including KEYNOTE-021 G, making the updated ITC relevant and more robust for decision making in comparison to the ITC submitted at the point of CDF entry. The submission describes that the KEYNOTE-189 FA data cut incorporated into the ITC provides an additional 8.3 months of data compared to the submission at the point of CDF entry.
Is it still the case that pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% TPS does not meet NICE's end-of-life criteria?	Clinical expert opinion elicited by MSD during the current appraisal, validated that a 24-month life expectancy in TPS ≥ 50% subgroup is not likely in many patients at all. Whilst expert input suggested that patients in the TPS ≥ 50% subgroup may live longer than those with TPS <50%, this is often not likely to exceed 12-18 months. In addition, expert opinion elicited during the technical engagement call of this current appraisal explained that median survival time for patients receiving single agent immunotherapy is likely to be less than 24 months. The expert input stated, whilst there may be some variation, a minority of patients will continue treatment up to 2 years. Clinical opinion sought by MSD suggests that they would value the option to give the pembrolizumab combination in the 1L, due to the known delayed effect of immunotherapy alone. Furthermore, whilst experts consider pembrolizumab monotherapy is an appropriate option for some patients, there are still patients within the TPS ≥50% subgroup whom the combination would be appropriate for. These patients would most likely have aggressive and centrally located disease. The option of

	pembrolizumab combination is also supported in specific cases of patients with TPS ≥50% by The Society for Immunotherapy of Cancer [1] Expert input during the technical engagement call stated, that whilst not a large number of patients would receive pembrolizumab combination in the TPS ≥50% subgroup, pembrolizumab combination does have a place and is used in some groups of patients who have bulky or central disease impinging on airways and at risk of not responding. Furthermore, it was described on the technical engagement call that pembrolizumab combination is and should used in critical patients to achieve maximum response. Moreover, the need to gain rapid control of the tumours is particularly relevant to the UK: according to the most recent report from the NHS, only 71.8% of patients with lung cancer receive their first treatment within the 62 days target after urgent GP referral[2] In the absence of UK real-world evidence, results from a retrospective study, which included adults with ECOG 0–1 initiating 1L pembrolizumab monotherapy on/after 24th October 2016, using datasets drawn from the Flatiron Health longitudinal database comprising EHR data of patients with cancer in the USA was analysed[3]. The restricted mean at 28.6 months (maximal survival length in the study cohort at database cut off) was [redacted] months while the median OS was 18.9 (14.9-25.5) months. Therefore, based on the above real-world evidence and clinical expert opinion, on balance this subgroup meets the EoL criteria.
Issue 3: Extrapolation of overall survival	
Is the log-logistic distribution or the generalised gamma distribution the most appropriate extrapolation of OS, for both the pembrolizumab combination and standard of care arms?	**Clinical plausibility** MSD suggests that the loglogistic distribution is more appropriate for the extrapolation of OS - for both arms - rather than the generalized gamma, because it results in more clinically plausible 5-year OS estimates for both arms. In terms of the chemotherapy arm, both parametric curves give similar estimates and they are both within the range expected for the chemotherapy arm (5-11%, as agreed in the TA557 FAD). In terms of the pembrolizumab combination arm, recent evidence suggests that the 5-year OS is much closer to the estimate of the log-logistic extrapolated curve. The KEYNOTE-001 study has the longest efficacy and safety follow-up for patients with treatment-naïve NSCLC treated with pembrolizumab monotherapy and recently reported a 5-year OS of 23.2% for treatment-naïve patients, further confirming high 5-year OS rate as well as durable response [4]. The KEYNOTE-024 study (pembrolizumab vs platinum based chemotherapy for untreated advanced NSCLC patients with TPS expression ≥50%) also reported high OS, 36-month OS of 43.7% and 42-month OS of

[redacted] The KEYNOTE-021G (KEYNOTE-021 cohort G long-term follow-up: 1L pemetrexed and carboplatin (PC) with or without pembrolizumab for advanced non squamous NSCLC) reported also a very high 3-year OS of [redacted]

Table 1. 1, 2, 5, 10 and 20-year OS – log-logistic extrapolation

	1-Y OS	2-Y OS	3-Y OS	5-Y OS
Pembro + Chemo	68.7%	46.2%	33.0%	**19.7%**
Trial Chemo	48.2%	25.9%	16.3%	**8.6%**

Table 2. 1, 2, 5, 10 and 20-year OS - generalised gamma extrapolation

	1-Y OS	2-Y OS	3-Y OS	5-Y OS
Pembro + Chemo	70.1%	46.5%	30.0%	12.1%
Trial Chemo	48.6%	26.9%	16.7%	8%

Additionally, clinical expert opinion elicited at the CDF entry point, as well as during the submission for the CDF exit and the technical engagement call, supports the assumption that 5-year OS of the pembrolizumab combination arm is expected to be closer to estimate yielded by the log-logistic curve rather than the generalised gamma curve. Finally, clinical opinion also confirmed that the difference of only 4% between the intervention and the control arm (yielded by the generalised gamma distribution) is not a plausible estimate and it is considered too low.

Statistical fitting

While the ERG stated: "*generalised gamma is equally important to consider alongside the log-logistic function*" they chose the generalised gamma for their base case as they argue that it "*provides a better statistical fit to the KEYNOTE-189 data*". The ERG cited a paper by Burnham and Anderson from 2004 (see page 34 of the ERG report) according to which models with a ΔAIC between 4 and 7 from the best-fitting curve have "considerably less support". Log-logistic had a ΔAIC from the best-fitting model of 4.9, but the generalised gamma model had a ΔAIC of 2 points and as a 'rule of thumb' the authors propose that these models with <2 points have 'substantial support'. [5]

	MSD suggests that it does not seem reasonable to use a rule of thumb, from a paper published in 2004, to make inferences for extrapolating survival for oncology treatments which merit their own individual statistical investigation and would plausibly be expected to have variation in survival trajectories. In support of this, MSD identified a more recent publication (2011) [6], from the same authors, which reads: "*Some of the early literature suggested that models were poor (relative to the best model), and might be dismissed if they had Δ>2. This arbitrary cutoff rule is now known to be poor, in general. Models where Δ is in the 2–7 range have some support and should rarely be dismissed*. " Additionally, as it is not clearly stated on the technical engagement report, MSD wants to highlight that the log-logistic is the best fitting curve for the SoC arm (both lower AIC and BIC statistics) but was ranking 5th and 4th (for the AIC and BIC respectively) in the pembrolizumab combination arm. In addition, the log-logistic provided more clinically plausible 5-year OS data as described above. Therefore, the log-logistic is the most appropriate curve for extrapolating the KEYNOTE-189 data. **Text inaccuracies** Finally, MSD would like to highlight the following inaccuracies on the draft technical report under Issue 3: • Page 14 states: "*The ERG noted that the log-logistic model was not the statistically best fitting model and highlighted the importance of considering alternative models for OS*" This sentence is partially inaccurate as the log-logistic model is the best statistical fitting curve for the chemotherapy arm (log-logistic had the lower AIC and BIC values) but not for the pembrolizumab combination arm (log-logistic was the 5th lower AIC and the 4th lower BIC). Therefore, the sentence should read: "*The ERG noted that the log-logistic model was the statistically best fitting model for the chemotherapy arm but not for the pembrolizumab combination arm and highlighted the importance of considering alternative models for OS*" • Page 14 states: "*Both of these models yield estimates of five-year OS that exceed the expected range for the SoC arm (5-11%, as discussed in the TA557 FAD)".* This sentence is inaccurate as the log-logistic and generalized gamma curves yield 5-year OS estimates of 8.6% and 8% respectively and therefore, they are both **within** the expected range of 5-11%. The sentence should read: "*Both of these models yield estimates of five-year OS that <u>do not</u> exceed the expected range for the SoC arm (5-11%, as discussed in the TA557 FAD)"* • Page 14 states: "*It is appropriate to use the Kaplan-Meier curve with the tail extrapolated using the generalised gamma rather than the log-logistic distribution…*". This sentence is stating a piecewise approach is preferred by the technical team however, both the ERG and MSD explored the fully fitted curves only, i.e. the whole KM curves, from time 0, were extrapolated rather than the tails for both arms. MSD suggests for clarity that the sentence reads: "*It is appropriate to*

	extrapolate the KM data using a fully-fitted generalised gamma distribution rather than a fully-fitted log- logistic distribution…"
Issue 4: Extrapolation of time-on-treatment	

Is the exponential distribution or the generalised gamma distribution the most appropriate extrapolation of time-on-treatment, for both the pembrolizumab combination and standard of care arms?

The goodness-of-fit statistics were considered for both arms (see table below). For the pembrolizumab combination arm, generalised gamma had the lower AIC and exponential the lower BIC. Similarly, for the chemotherapy arm, generalised gamma had the lower AIC and exponential the lower BIC.

Since both curves had good statistical fitting, visual inspection was also considered for both arms. For the pembrolizumab combination arm, both curves provide similar fit however, it seems that the exponential curve is closer to the KM data between 6 months and 1 year. For the chemotherapy arm, both curves are almost overlapping so there is no clear difference in visual fit.

	Pembrolizumab combination		Chemotherapy arm	
	ITT		ITT	
Fitted Function	AIC	BIC	AIC	BIC
Exponential	3770.2	**3774.3**	1737.1	**1740.4**
Weibull	3772.2	3780.2	1736.5	1743.1
LogNormal	3904.2	3912.2	1812.8	1819.5
LogLogistic	3837.2	3845.2	1782.7	1789.3
Gompertz	3769.7	3777.7	1739.1	1745.7
GenGamma	**3764.8**	3776.8	**1731.2**	1741.2

	[redacted]

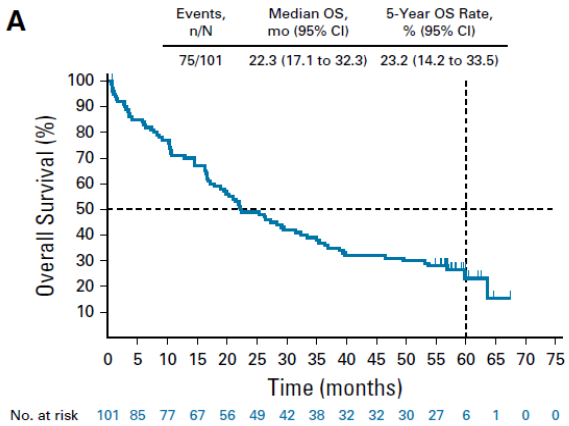
[redacted]

As the ERG also pointed out in their report, the choice of an exponential curve assumes proportional hazards. Please find the cumulative hazard plots for both treatment arms in the figure below. While the curves seem to deviate from each other, there is no crossing of the curves, suggesting that proportional hazards may hold and therefore the exponential curve may also be an appropriate option for extrapolating the ToT. In any case, the choice of the generalised gamma over exponential curve for the ToT has minimal impact on the ICER as it increases to [redacted] (from [redacted] in the base case).

	[redacted]	

Issue 5: Time horizon	
Are all differences in costs and effects attributable to pembrolizumab combination likely to be captured in a 20-year time horizon?	Since a small proportion of patients are still alive at the 20-year time point when using the log-logistic curve for extrapolation, MSD suggests that a time-horizon of 25 years in the model is more appropriate to capture all important differences in cost or QALYs between the two treatments.
Issue 6: Treatment effect duration	
Is a 2-year, 3-year or 5-year duration of treatment effect for pembrolizumab appropriate?	MSD acknowledges that the duration of treatment effect is an area of uncertainty for new immunotherapies. In previous technology appraisals in this disease area, NICE recognized that due to the mode of action of the immunotherapies, it is biologically plausible for the treatment effect to continue after treatment. For consistency with the original submission at the CDF entry point (TA557), but also in more recent Tas such as TA584 for atezolizumab in combination in 1L NSCLC, and TA484 for nivolumab 2L NSCLC, a 5-year treatment effect (from treatment initiation) was implemented in the base case. (However, MSD would like to point out that committee has also accepted a longer treatment effect duration eg atezolizumab in 2L NSCLC (TA520) where the FAD stated: “the committee considered that the treatment effect was unlikely to last more than 5 years *after treatment had stopped*”. This treatment effect equates to 7 years post treatment initiation.)
Is there any additional evidence which could be used to inform the duration of treatment effect for pembrolizumab in this indication?	Since the TA557, more mature evidence in NSCLC have been published and they all confirm the potential for a sustained treatment effect of pembrolizumab.

The longest-term data come from **KEYNOTE-001**[4] median 60.6 months of follow-up). The KM curve shows a plateau after 40 months and a 5-year OS estimate of 23.3% in treatment naïve patients (see figure below).

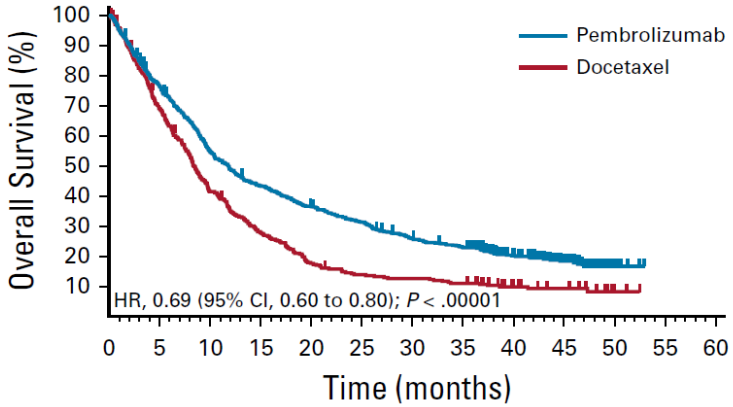


Of the 60 patients who received 2 or more years of treatment with pembrolizumab, 46 were alive at data cutoff, with an estimated 5-year OS rate of 78.6% in the treatment-naive group. Among patients who completed 2 or more years of pembrolizumab therapy, 12 (86%) of 14 patients in the treatment-naïve group experienced an objective response. Median DOR was 52.0 months (range, 10.2 to 55.7+ months). Seven treatment-naive patients (58%) had an ongoing response at data cutoff. In addition to the 54 patients with a response who completed 2 or more years of treatment (of 145 patients with a response), 6 patients with stable disease completed 2 or more years of treatment (202 patients with stable disease), 2 of whom had died.

Evidence is also available from **KEYNOTE-010** [7] (2L NSCLC >1%) with a median follow up of 42.6 months.

B

	Overall survival events, n/N (%)	Median overall survival, months (95% CI)	36-month overall survival rate, % (95% CI)
Pembrolizumab	548/690 (79.4)	11.8 (10.4 to 13.1)	22.9 (19.8 to 26.1)
Docetaxel	295/343 (86.0)	8.4 (7.6 to 9.5)	11.0 (7.9 to 14.7)

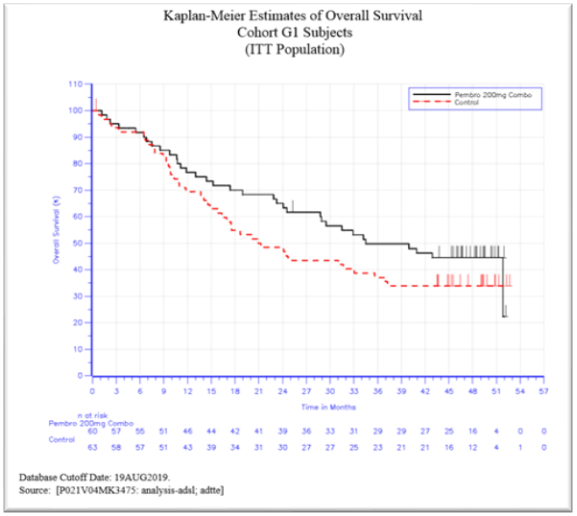


No. at risk:

Pembrolizumab	690	523	374	295	248	211	171	151	86	45	5	0	0
Docetaxel	343	226	135	90	57	44	40	35	20	13	2	0	0

As of the March 16, 2018, data cutoff date, a total of 79 patients had completed 35 cycles/2 years of pembrolizumab, with a median follow-up of 43.4 (range, 35.7-49.8) months. Objective response rate among patients who completed 35 cycles was 94.9%, with ongoing response in 48 patients (64.0%); 72/79 patients (91.0%) remained alive at the data cutoff date. OS rates at 12 and 24 months after completing 35 cycles were 98.7% (95% CI, 91.1% to 99.8%) and 86.3% (95%CI, 72.7%to 93.4%).

KEYNOTE-021G [8] reported long term data [redacted]. OS and PFS HRs favoured pembrolizumab + pemetrexed and carboplatin (PC) and 3-year rates were higher with pembrolizumab + PC vs PC. The OS HR was 0.71(95% CI: 0.45, 1.12; nominal p= [redacted]) in favour of the pembrolizumab/pemetrexed combo. The median OS for the pembrolizumab/pemetrexed combo was 34.5months (95% CI: 24.0, NR) compared to 21.1 (95% CI: 14.9, 35.6) for the control.

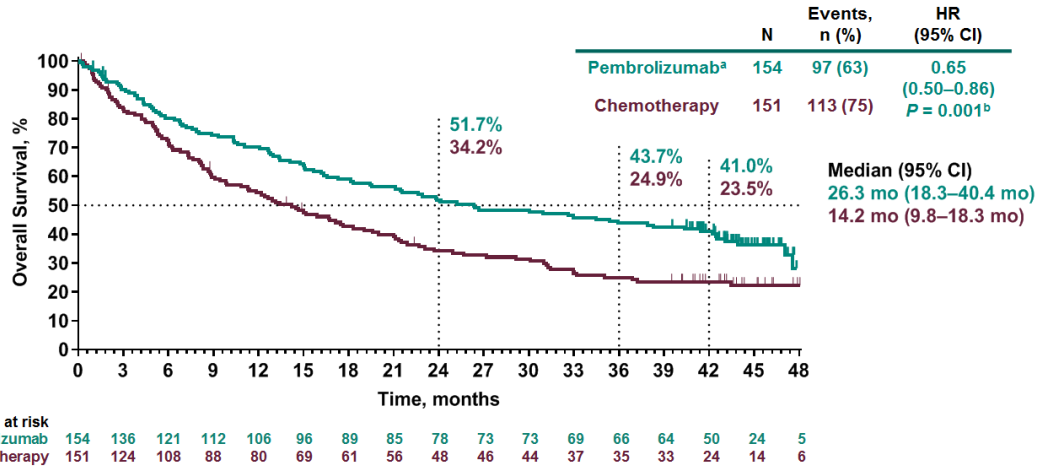


[redacted]

KEYNOTE-024 [9] (1L NSCLC, TPS≥50%) reported a 3-year survival update of pembrolizumab versus platinum-based chemotherapy (median follow up of 44.4 months). Again, KM shows a plateau in the OS approximately after 2 years with a sustained effect.

Reck KN024 WCLC 2019

Overall Survival: Updated Analysis



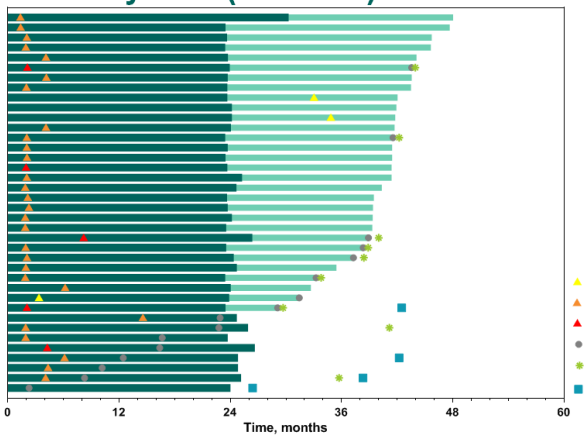
[a]Effective crossover rate from chemotherapy to anti–PD-L1 therapy, 64.9% (98 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 21 patients received subsequent anti–PD-L1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-L1 therapy). [b]Nominal *P* value.
Data cutoff: February 15, 2019.

At the date of the cut off, 27 out of 38 patients (71%) who completed 35 cycles of pembrolizumab continue to have disease control without requiring any treatment.

Reck KN024 WCLC 2019

Treatment Duration and Time to Response

35 Cycles (2 Years) of Pembrolizumab Completed[a]



	35 Cycles (2 Years) of Pembrolizumab N = 38
DOR ≥12 mo,[b] n (%)	27 (87)
DOR ≥24 mo,[b] n (%)	25 (81)
Ongoing response, n (%)	22 (58)

At the data cutoff for this analysis, 27 out of 38 patients (71%) continue to have disease control without requiring any treatment

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. [a]Dark green bars indicate treatment duration and light green bars indicate first course follow-up duration. Follow-up was defined as the time to progression or last non-progression assessment by investigator. Response was assessed per RECIST version 1.1 by investigator review. [b]From Kaplan-Meier method for censored data. Data cutoff: February 15, 2019.

Issue 7: Health-related quality of life	
What is the most appropriate approach to incorporate both progression status and time-to-death within the estimation of utilities?	During the TA557 the committee preferred a combined method to fully capture the quality-of-life changes for people with NSCLC but the FAD did not explicitly clarify which of two approaches was preferred. MSD, for consistency with the committee's preference at the CDF entry point, adopted one of the combined methods and selected the time-to-death with the progression decrement applied as the approach to death reflects better the decline in cancer patients' quality of life and also this method utilizes more health states and potentially offers a better fit to patient data. Additionally, the proximity to death approach seemed to be accepted by NICE in TA584 - Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. MSD would like to clarify that the combined method has limitations as appears to double-count utility decrements and under-estimates utility values and cost-effectiveness for patients within the trial. The combined method essentially adds a further

	utility decrement based on either the percentage of patients in a cycle who are <360 days from death (if modeling progression-based utilities) or with progressed disease (if modelling time-to-death utilities). The double counting occurs because the TTD <360 days patient utilities and progressed disease utilities already implicitly fully reflect a decrement associated with progressed disease or time-to-death, respectively, based on the fraction of patients in each state who fall within a given progression/time to death category. Therefore, MSD suggests that the TTD approach without the progression decrement is more appropriate for this indication and has been accepted by the committee before.

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NICE National Institute for Health and Care Excellence

Clarification question raised by the Chair of the committee during the Technical Engagement call with MSD: How are the costs and benefits of 2L treatments in the intervention arm taken into account in the cost effectiveness model?

MSD would like to highlight that this question was not raised at any point during TA557 and it was not considered as an area of uncertainty that needed to be resolved/updated through additional data collection during the CDF. Therefore, it was not part of the FAD at the entry point neither part of the data collection agreement (DCA) document or the Terms of Engagement (ToE) document MSD received. However, MSD has provided below data from Final Analysis about the utilization of 2L therapies in both arms as well as the mean duration of treatment for these therapies. Finally, a scenario analysis is presented where the costs of 2L IOs were implemented for both arms however, this is caveated with the robustness of this analysis.

Utilization of subsequent therapies after discontinued/completed from study treatment is presented in Table 1 for the overall population.

Table 1: Utilization of New Subsequent Therapies - Final Analysis cut-off

Utilization of New Subsequent Therapies
(All-Subjects-as-Treated Population)

Study: 3475-189	Patients with Subsequent Therapies	
Line Therapy	Pembro Combo N = 405	Control N = 202
Patients with one or more subsequent therapies	[redacted]	[redacted]
2L	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]
docetaxel	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]
docetaxel+nintedanib	[redacted]	[redacted]
pemetrexed disodium	[redacted]	[redacted]
carboplatin+pemetrexed disodium	[redacted]	[redacted]
docetaxel+ramucirumab	[redacted]	[redacted]
carboplatin	[redacted]	[redacted]
atezolizumab	[redacted]	[redacted]
bevacizumab+paclitaxel	[redacted]	[redacted]
docetaxel+nintedanib esylate	[redacted]	[redacted]
gemcitabine	[redacted]	[redacted]
crizotinib	[redacted]	[redacted]
paclitaxel	[redacted]	[redacted]
carboplatin+paclitaxel	[redacted]	[redacted]
carboplatin+vinorelbine tartrate	[redacted]	[redacted]
cisplatin+pemetrexed disodium	[redacted]	[redacted]
erlotinib hydrochloride	[redacted]	[redacted]
alectinib	[redacted]	[redacted]
anti-OX40 monoclonal antibody (unspecified)+avelumab+utomilumab	[redacted]	[redacted]
carboplatin+gemcitabine	[redacted]	[redacted]
glesatinib	[redacted]	[redacted]
osimertinib	[redacted]	[redacted]

pembrolizumab+pemetrexed disodium	[redacted]	[redacted]
vinorelbine tartrate	[redacted]	[redacted]
Akt kinase inhibitor (unspecified)	[redacted]	[redacted]
B-000056613+pembrolizumab	[redacted]	[redacted]
adenosine receptor alpha2A antagonist (unspecified)	[redacted]	[redacted]
adenosine receptor alpha2A antagonist (unspecified)+atezolizumab	[redacted]	[redacted]
anti-AXL receptor tyrosine kinase antibody drug conjugate (monomethyl auris	[redacted]	[redacted]
anti-FAP monoclonal antibody interleukin 2 fusion protein	[redacted]	[redacted]
anti-ICOS monoclonal antibody (unspecified)+nivolumab	[redacted]	[redacted]
bevacizumab+carboplatin+paclitaxel	[redacted]	[redacted]
bevacizumab+docetaxel	[redacted]	[redacted]
bevacizumab+erlotinib hydrochloride	[redacted]	[redacted]
bevacizumab+paclitaxel albumin	[redacted]	[redacted]
binimetinib+palbociclib	[redacted]	[redacted]
carboplatin+erlotinib hydrochloride+pemetrexed disodium	[redacted]	[redacted]
carboplatin+etoposide	[redacted]	[redacted]
carboplatin+pembrolizumab+pemetrexed disodium	[redacted]	[redacted]
docetaxel+nintedanib+ret proto-oncogene inhibitor (unspecified)	[redacted]	[redacted]
docetaxel+nivolumab	[redacted]	[redacted]
glutaminase inhibitor (unspecified)+nivolumab	[redacted]	[redacted]
ipilimumab+nivolumab	[redacted]	[redacted]
mitomycin+vinorelbine tartrate	[redacted]	[redacted]
mocetinostat	[redacted]	[redacted]
osimertinib mesylate	[redacted]	[redacted]
paclitaxel+ramucirumab	[redacted]	[redacted]
sitravatinib+tislelizumab	[redacted]	[redacted]
tepotinib	[redacted]	[redacted]

2L includes pembrolizumab monotherapies from subjects who crossed over from Control arm to pembro mono treatment or from Pembro Combo subjects who were re-treated with pembro mono in the second course phase allowed by protocol (Database Cutoff Date: 20MAY2019).

The benefit of any drug use for both arms during the KEYNOTE-189 trial was taken into account in the KM dataset and is expected to be reflected in the efficacy and the QALY's.

NICE's reference case suggests that the treatments need to reflect "interventions routinely used in the NHS, including those regarded as current best practice" and perspective on costs need to be the one from the NHS. Therefore, based on clinical expert opinion and NICE's treatment pathway, the use of 2L immunotherapies in the intervention arm is not clinical practice. NICE has consistently, so far, taken a pragmatic approach in all 1L NSCLC indications were 2L treatments were adjusted/reweighted to reflect the NHS clinical practice. For example, in the TA584 (atezolizumab in combination for the 1L NSCLC) the committee concluded that the company's revised analyses that submitted at consultation were more appropriate than analyses including treatment options that are not routinely commissioned in the NHS in England. More specifically, NICE's preferred assumption about the subsequent therapy was docetaxel after atezolizumab combination even though there was use of 2L IO in the atezolizumab combination arm (11% received nivolumab and 9% bevacizumab)

For illustrative purposes, MSD provided a scenario analysis were subsequent 2L IO treatments were included in the intervention arm – and updated for the control arm. Please note that due to the guidance from NICE for the CDF drugs, nivolumab was not taken into consideration and the proportion was reweighted to the other therapies equally. The duration

of these treatments was also drawn from the KEYNOTE-189 trial:

Table 2. Duration of New Subsequent Therapies Subjects Who Discontinued or Completed Study Treatment (All-Subjects-as-Treated Population)

Treatment Duration (days)	Pembro Combo (N=388)		Control (N=201)		Pooled (N=589)	
	n (m)[a]	Mean (SE)	n (m)[a]	Mean (SE)	n (m)[a]	Mean (SE)
2L	200 (279)		125 (132)		325 (411)	
I-O drugs[b]	47 (47)	141.3 (24.2)	109 (109)	168.7 (20.9)	156 (156)	160.4 (16.3)
Maintenance drugs[c]	33 (33)	153.6 (36.0)	6 (6)	120.0 (68.8)	39 (39)	148.4 (32.0)
Chemo drugs	129 (139)	108.7 (10.0)	9 (9)	86.1 (41.9)	138 (148)	107.3 (9.7)
Others	57 (60)	159.6 (17.9)	7 (8)	146.0 (48.4)	64 (68)	158.0 (16.7)

a: Every subject is counted a single time for each applicable row and column.; m is the number of medication records

b: I-O drug includes atezolizumab, nivolumab, pembrolizumab, avelumab, and their combined therapies

c: Maintenance drug includes bevacizumab, pemetrexed, and their combined therapies

For the scenario analysis, the distribution of the medicines was as per table below:

Table 3. Distribution of 2L therapies

Post-discontinuation regimen (dose)	Pembrolizumab + Chemotherapy Arm	Chemotherapy Arm - Active
Distribution of 2nd line therapies		
Carboplatin (400 mg) + Gemcitabine (1250 mg/m^2)	[redacted]	
Carboplatin (400 mg) + Pemetrexed (500 mg/m^2)	[redacted]	
Cisplatin (75 mg/m^2) + Pemetrexed (500 mg/m^2)	[redacted]	
Docetaxel (75 mg/m^2)	[redacted]	[redacted]
Docetaxel (75 mg/m2) + Nintedanib (200 mg)	[redacted]	
Atezolizumab	[redacted]	[redacted]
Pembrolizumab (200 mg)	[redacted]	[redacted]
% Total	[redacted]	[redacted]

The impact on the ICER is illustrated on the table below:

Table 4. Base case results for Overall Population

Base case results (pembrolizumab + chemotherapy vs trial chemotherapy arm) for Overall Population								
Comparators	**Total costs**	**Total LYs**	**Total QALYs**	**Incremental costs**	**Incremental LYG**	**Incremental QALYs**	**ICER vs. baseline (QALYs)**	**ICER incremental (QALYs)**
Trial Chemotherapy Arm	[redacted]	[redacted]	[redacted]					
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

This scenario analysis shows that the impact in the ICER form the base case was very small [+£2108] however, MSD would like to highlight that this scenario is not an appropriate nor a robust method for decision-making because the NHS would not ultimately accrue the costs of 2L IO use in the intervention arm since it is not clinical practice as confirmed by the clinical expert at the technical engagement call.

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (CDF Review of TA557) [ID1584]

ERG Review of Company's Response to Technical Engagement Response

1 April 2020

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1. INTRODUCTION

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (CDF Review of TA557) [ID1584].

Each of the issues outlined in the technical report are discussed in further detail in Section 3. Although the company indicated revisions to their base case, no updated company base case analyses were presented by the company in its TE response. Based on the response to the technical engagement report the ERG has provided updated company and ERG base case results in Section 2.

2. UPDATED COMPANY AND ERG BASE CASE ANALYSES

In response to the technical engagement report, the company did not present a revised base case analysis.

In respect of the company base case the ERG noted the following from the technical engagement response:

- Issue 5 the company agreed a 25-year time horizon; and
- Issue 7 the company changed its preference in respect of the approach to utilities, favouring a time to death approach but with no decrement associated with progression.

The ERG has provided updated company base case results in Table 1 taking the above factors into account.

Table 1: Updated company base case analyses

Suggested changes to the company base case ICER	Pembro + chemotherapy		Chemotherapy		ICER £/QALY	Cumulative difference
	QALYs	Costs	QALYs	Costs		
Company base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Suggested changes to the company base case ICER	Pembro + chemotherapy		Chemotherapy		ICER £/QALY	Cumulative difference
	QALYs	Costs	QALYs	Costs		
1. 25-year time horizon (Issue 5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility option						
2. Time-to-death approach only (Issue 7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

In respect of the ERG base case the ERG noted the following from the technical engagement response:

- Issue 5 the ERG considers a 25-year time horizon may be more appropriate to capture all costs and health benefits; and,
- Issue 6 the ERG agreed a treatment waning effect applied over three to five years was a reasonable assumption and was aligned to the three to five years outlined in TA557.

The ERG has provided updated company base case results in Table 2 taking the above factors into account.

Table 2: Updated ERG base case analyses

Changes to the ERG base case ICER	Pembro + chemotherapy		Chemotherapy		ICER £/QALY	Cumulative difference
	QALYs	**Costs**	**QALYs**	**Costs**		
ERG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
1. 25-year time horizon (Issue 5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TWE						
2. TWE applied between 3 – 5 years (Issue 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

3. ERG REVIEW OF KEY ISSUES

Issue 1: Comparison with other chemotherapy

Is the company's approach to comparing pembrolizumab combination with other chemotherapy treatments representative of clinical practice?

As noted in the ERG report, the company did not present a comparison of pembrolizumab combination with other chemotherapy treatments (docetaxel, gemcitabine, paclitaxel or vinorelbine as monotherapy), with carboplatin or cisplatin, with or without pemetrexed maintenance therapy) by means of an NMA or an updated systematic literature review (SLR). The company's justification was that the results of the NMA, submitted as part of CS1[1] at the point of CDF entry, showed no statistically significant difference between the platinum doublet chemotherapy interventions commonly used in UK clinical practice. While the ERG accepted the rationale provided in the company submission, it also noted that the degree to which new evidence would have changed the conclusions of the NMA was unclear.

Clinical feedback given at the time of TA557, was that platinum + docetaxel, platinum + paclitaxel, and platinum + paclitaxel + bevacizumab were not commonly used in UK clinical practice. In its response to technical engagement, the company noted that it had received clinical expert opinion which indicated that there have been: "no significant publications, regarded of high importance, disseminated within the clinical community which would result in a change in the assumption that the comparator within the pivotal trial is considered the most relevant." The ERG was unable to elicit further clinical input of its own at this time but highlight consistency in the feedback received during this update review, and alignment with advice received at the point of CDF entry (CS1); i.e. that there has been no change in backbone chemotherapy in the management of first-line non-squamous NSCLC.

In its response, the company also reported that an updated literature search (to October 2019) had been completed which had followed the same search and methodology as for the SLR underpinning the submission at the point of CDF entry (CS1). While the methods (and related ERG critique) had been documented previously in CS1, the company did not report findings from its updated SLR in its response (e.g. absence of a PRISMA flow diagram documenting the study selection process – numbers retrieved, studies excluded at title/abstract and full text). A tabulated list of what the ERG assumed to be studies included at full text was provided by the company together with a comment as to the applicability of the study to this CDF review. The

ERG concurred with the company's view that none of the evidence listed in the table in the company's TE response would have contributed additional evidence for this appraisal.

Issue 2: Comparison with pembrolizumab monotherapy

Is the additional data used to update the indirect treatment comparison (ITC) enough to reduce the uncertainty in the overall survival estimates for pembrolizumab combination therapy compared with pembrolizumab monotherapy?

The ERG maintains its earlier critique in respect of the OS estimates from the ITC conducted by the company comparing pembrolizumab combination therapy with pembrolizumab monotherapy.

To summarise, the ERG noted that the ITC incorporated evidence from four trials (KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, KEYNOTE-021G), thus integrating all available trial evidence. Of note, KEYNOTE-189 provided an additional [redacted] months of follow-up data relative to that presented in the submission at the point of CDF entry (CS1).

The ERG judged that the methods used to undertake the ITC were broadly appropriate. Findings of the ITC suggested that pembrolizumab combination therapy offered a numerical, but not statistically significant, improvement in OS as compared to pembrolizumab monotherapy (HR=[redacted]). The ERG noted that tests of proportional hazards assumptions were not presented, so it was not possible for the ERG to assess how appropriate these HRs are as summary estimates. However, the ERG considered that the assumption appeared broadly appropriate for analyses of OS.

Is it still the case that pembrolizumab combination compared with pembrolizumab monotherapy for people whose tumours express at least a 50% TPS does not meet NICE's end-of-life criteria

Recent RWE from the US (Velcheti et al., 2019[2]) estimates median survival in pembrolizumab monotherapy patients for those with a TPS >50% is between 18.9 months (range 14.9 – 25.5) and 19.1 months (range 12.6 – NR) as derived from the EHR and Spotlight registries, respectively.[2] While these estimates are close to a 24-month median, it may be the case that mean OS is greater than 24 months. This is reinforced with the generalisation that immunotherapies will provide a 'plateau' of long-term survival for some patients, resulting in a larger mean than median in extrapolated survival. Moreover, the 24-month criterion states that the treatment should be indicated for patients with "a short life expectancy, normally less than 24 months", thus a median of close to this value implies that nearly half of patients will live

longer than 24 months (and in the case of pembrolizumab, perhaps for substantially longer than 24 months based on the expected plateau in survival).

Further to this, evidence from KEYNOTE-001 provides long-term survival estimates of pembrolizumab monotherapy patients in the TPS>50% subgroup. Outcomes of this study indicated a median OS of 35.4 months, indicating the median survival alone would be above the threshold considered relevant to meet NICEs end-of-life criteria.

Despite limitations with RWE, and acknowledging that KEYNOTE-001 may provide optimistic survival estimates (for reasons listed in relation to Issue 3), the ERG considered it reasonable to assume that median survival probably lies within this range and is therefore close to 24 months while mean survival would be expected to be >24 months with pembrolizumab monotherapy in this indication.

Noteworthy is that within the company base case for the TPS>50% population, the company's model results in [redacted] life years accrued in the pembrolizumab monotherapy arm (reduced to [redacted] when discounting at 3.5%) – both above 24 months. In TA557 the committee concluded that "pembrolizumab combination compared with pembrolizumab monotherapy in people whose tumours express a tumour proportion score of at least 50% did not meet the end-of-life criteria" (NICE, TA557: FAD, p.18).

Issue 3: Extrapolation of overall survival

Is the log-logistic distribution or the generalised gamma distribution the most appropriate extrapolation of OS, for both the pembrolizumab combination and standard of care arms?

Using guidance outlined in TSD 14, the ERG still believes that both curves (the log-logistic and the generalised gamma) may be plausible extrapolations of OS. This is based on an amalgamation of statistical fit, visual fit and what appears to be plausible in the longer term. While the ERG acknowledges that the parametric selections for the chemotherapy arm are relatively comparable, the selection in the pembrolizumab + chemotherapy arm results in substantially different ICERs. The ERG's preferred approach (applying a generalised gamma curve with a gradual TWE from two to five years) is compared to the company base-case curves (log-logistic with an instant TWE at five years) is presented in Figure 1.

Figure 1: Company base case curve selection with 5-year TWE compared to ERG scenario applying generalised gamma with a gradual 2-5 year TWE

The company drew on alignment between KEYNOTE-189 and the prior study KEYNOTE-001 to support long-term estimates of OS for patients receiving pembrolizumab + chemotherapy. However, the ERG considers this rationale to be flawed due to inconsistencies across the trials. Several limitations to this line of argument are:

- **Intervention:** KEYNOTE-001 considers pembrolizumab monotherapy not pembrolizumab + chemotherapy combination therapy.
- **TPS:** There is an imbalance in TPS across the two studies (as shown in Table 3). In KEYNOTE-001, 86.8% of patients with an evaluable TPS were >1% in the treatment naïve setting. In the KEYNOTE-189 study this was 67.2%. Given TPS is associated with higher OS, it is anticipated that this would have an impact on the comparability of the studies with the expectation all other things equal, patients studied in KEYNOTE-001 would achieve better outcomes (given their increased capacity to derive benefit through having [on average] a higher TPS) versus those studied in KEYNOTE-189.

Table 3: TPS score differences between KEYNOTE-189 and KEYNOTE-001

TPS score	KEYNOTE-189		KEYNOTE-001	
>50	132	34.11%	27	29.67%
1-49%	128	33.07%	52	57.14%
<1%	127	32.82%	12	13.19%

Abbreviations: TPS, tumour proportion score

- **Dosing:** The dosing of KEYNOTE-001 was different and changed throughout the study - Patients were administered 2 mg/kg every three weeks of 10 mg/kg every two or three weeks with patients treated until progression. The KEYNOTE-189 study administers 200 mg every three weeks for up to 36 cycles. In April 2016 there was a protocol amendment to KEYNOTE-001 which then changed the dose to 200 mg every three weeks, and allowed patients with PR or SD to stop treatment with the option of future retreatment. This would not be considered in UK practice and as the details of retreatment are not known by the ERG, the impact this would have on outcomes of the KEYNOTE-001 are unclear. Notably, 14% of the treatment naïve arm in KEYNOTE-001 received two or more years of treatment with pembrolizumab, which is not aligned with the KEYNOTE-189 protocol, hindering the comparability of these studies further. There is no evidence currently known to the ERG to understand the impact of stopping treatment versus continuing. Therefore, it is unclear whether patients in KEYNOTE-001 could have continued to derive additional benefit from continued use of pembrolizumab, thus further confounding estimates of OS.

- **Response:** The definition of (overall response) OR changed throughout the study – KEYNOTE-001 initially measured response by independent central review as per the RECIST 1.1 criteria. This was aligned with KEYNOTE-189. After the protocol amendment the independent central assessment ceased and response was assessed by investigators per irRC. Results from the KEYNOTE-001 study indicated that initial results for the irRC was higher than the investigator assessment particularly among the treatment naïve patients, indicating that there is an inconsistency in outcomes across this trial alone prior to any comparison with other trials. Further to this in the longer-term data of KEYNOTE-001 performance (measured according to OR) was only assessed every six months post three-years, limiting the granularity of the results which can be interpreted from KEYNOTE-001.

- **Consistency in survival estimates:** Data from KEYNOTE-001 exhibit OS estimates of 49%, 37% and 31% for two, three, and four years, respectively. Comparing the company's modelled base case outcomes naively to the KEYNOTE-001 (as the company have done), the results of KEYNOTE-001 indicate that pembrolizumab monotherapy outperforms pembrolizumab + chemotherapy (modelled log-logistic curve with a TWE at five years produces survival of [redacted], [redacted] and [redacted] for two, three, and four years respectively). These results are contradictory to the company's output for the ITC, which suggest that pembrolizumab combination offers a substantial PFS and OS benefit with HRs of [redacted] and [redacted], respectively.

Based on these limitations the ERG believes that the KEYNOTE-001 and KEYNOTE-189 studies are not directly comparable, and therefore the KEYNOTE-001 cannot be reliably used to support a choice between the log-logistic and generalised gamma curves for OS within the cost-effectiveness model. Any inferences made on the pattern of survival expected in KEYNOTE-189 based on KEYNOTE-001 should be made with extreme caution.

While the ERG notes that at the time of CDF entry clinicians may have preferred the estimates provided by the original log-logistic curve, new parametric survival curves have been produced with more mature data and hence survival estimates have changed. Therefore, although broad comparisons can be drawn, it is entirely reasonable and plausible that clinical advice might evolve. Without references and details of the clinical validation undertaken by the company with the new data, the ERG cannot confirm which curve clinicians consider most appropriate. The ERG acknowledges that there is uncertainty and has elected to use the generalised gamma in its preferred base case due to the absence of evidence to reject this model, and to ensure the committee can easily see the impact of the curve selection on both estimates of life-years gained and the ICER. Without rationale to exclude either curve, and with the selection impacting the ICER (increasing the ICER to above a £50,000 WTP threshold), the ERG recommends that the committee should seek clinical feedback on the appropriate choice of curves for both arms of the model (alongside the TWE) and discuss the appropriateness of the corresponding survival predictions as a committee.

Issue 4: Extrapolation of time-on-treatment

Is the exponential distribution or the generalised gamma distribution the most appropriate extrapolation of time-on-treatment, for both the pembrolizumab combination and standard of care arms?

In partial agreement with the company, the ERG acknowledged that both curve selections (exponential and generalised gamma) fit the data relatively well. However, the company stated that the exponential may be a reasonable fit due to proportional hazards holding. The cumulative hazard plot presented by the company shows a clear change in gradient of the pembrolizumab combination curve at just over 100 weeks. This corresponds to the maximum treatment duration of pembrolizumab (36 cycles – two years). Based on the stopping rule, the ERG believes that the flexibility in the generalised gamma curves offers a better selection for ToT. The curves provide a good visual and statistical fit to the data without requiring unnecessary and potentially inaccurate assumptions around proportional hazards, particularly for an immunotherapy + chemotherapy combination where treatment durations are expected to be different.

In response to this issue, the company also commented on the impact of the choice of curve on the ICER: *"In any case, the choice of the generalised gamma over exponential curve for the ToT has minimal impact on the ICER as it increases to [redacted] (from [redacted] in the base case)."* [redacted]

Issue 5: Time horizon

Are all differences in costs and effects attributable to pembrolizumab combination likely to be captured in a 20-year time horizon?

The ERG considered that if selecting the generalised gamma curves for OS, then a 20-year time horizon would adequately reflect all costs and effects attributable to pembrolizumab chemotherapy versus chemotherapy. If the log-logistic extrapolation is considered more relevant for decision-making purposes then a 25-year time horizon should be adopted. The ERG is satisfied that a time-horizon of 25 years would ensure all costs and benefits are captured in either OS curve selection – in the case of the generalised gamma curve, the additional five years leads to the accrual of an additional [redacted] QALYs and [redacted] in costs (ERG's preferred base-case analysis).

The ERG note that the company did not provide an updated base case and has provided results incorporating this update in Section 2.

Issue 6: Treatment effect duration

Is a 2-year, 3-year or 5-year duration of treatment effect for pembrolizumab appropriate?

The ERG understands that the TWE is an area of uncertainty across many cancer immunotherapy appraisals and evidence to inform estimates is limited. The ERG consider that a gradual approach is more appropriate to consider compared to considering an instant change in hazards, as the former approach avoids an abrupt change in hazards which is unlikely to be clinically plausible. The ERG considered a two- to five-year gradual TWE applied in its initial base case, though the ERG understands the technical team's preference to apply the gradual approach between three years and five years. Given the original estimates at the point of CDF entry were three and five years, applying a gradual effect between the two timepoints may also be reasonable.

The ERG have provided an updated ERG base case incorporating this for which results are provided in Section 2.

Is there any additional evidence which could be used to inform the duration of treatment effect for pembrolizumab in this indication?

The company presented data from other trials in the broader NSCLC population including: KEYNOTE-001, KEYNOTE-010, KEYNOTE-021, and KEYNOTE-024 (refer to Table 4 comparison with KEYNOTE-189 – results presented in company TE response). As described in relation to Issue 3, the ERG has a number of concerns with the relevance of KEYNOTE-001 specifically. However, similar limitations may also be highlighted for the other three studies (KEYNOTE-010, KEYNOTE-021, and KEYNOTE-024).

Table 4: Additional evidence (compared with KEYNOTE-189)

Study	Population	Interventions evaluated	Median study follow-up
KEYNOTE-189	**Previously untreated, metastatic non-squamous NSCLC without sensitising EGFR or ALK mutations**	**Pembrolizumab 200 mg Q3W +pemetrexed + platinum-based chemotherapy for 4 cycles vs placebo 200 mg Q3W +pemetrexed + platinum-based chemotherapy for 4 cycles**	**18.8 months**

Study	Population	Interventions evaluated	Median study follow-up
KEYNOTE-001	Locally advanced or metastatic NSCLC (firstline and previously treated)	Pembrolizumab 2 mg/kg/ Q3W **vs** pembrolizumab 10 mg/kg Q3W **vs** pembrolizumab 10 mg Q2W	60.6 months
KEYNOTE-010	Previously treated PD-L1 positive (>1% TPS) NSCLC	Pembrolizumab 2 mg/kg, PD-1 inhibitor 10 mg/kg; docetaxel 75 mg/m^2	42.6 months
KEYNOTE-021G	Previously untreated, Stage IIIB or IV, non-squamous NSCLC without targetable EGFR or ALK genetic aberrations	Pembrolizumab 200 mg + carboplatin AUC 5 mg/ml + pemetrexed 500 mg/m^2 Q3W then pembrolizumab for 24 months + indefinite pemetrexed maintenance therapy; 4 cycles of carboplatin + pemetrexed alone followed by indefinite pemetrexed therapy	[redacted]
KEYNOTE-024	Advanced NSCLC PD-L1 TPS ≥50%	Pembrolizumab 200 mg Q3W (up to 2 yrs); platinum-based chemotherapy (4 to 6 cycles)	44.4 months

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; TPS, tumour proportion score; yrs, years

Issue 7: Health-related quality of life

What is the most appropriate approach to incorporate both progression status and time-to-death within the estimation of utilities?

As part of TA557 two methods were explored which incorporated both progression status and time-to-death within the estimation of utilities:

1. Progression based utilities with a decrement applied in the last year of life (Approach 1)

2. Time-to-death utilities with a decrement applied to account for progression (Approach 2)

As highlighted within the ERG report, both methods have limitations (ERG report: section 4.1.6). The company indicated within their response that they believed their initial approach to modelling utilities within the base case at the point of submission should be changed in favour of a different approach, applying a time-to-death decrement with no progression-based disutility (the ERG noted here that this approach was submitted previously in TA557 and was not considered relevant). The ERG was unclear as to why this change in approach has been undertaken, particularly as no new evidence was presented. Given the committee and clinical experts in TA557 suggested the both progression and time-to-death were important to a

patient's HRQOL, the ERG still believe the combined approach is reasonable. At the time of CDF entry, the committee preference at the time of TA557 was Approach 1.and the committee noted that there were some issues with the time-to-death approach, with a lot of data not available to analyse because they don't quality for any of the time-to-death health states (TA557 FAD: p.14). As there is no new evidence or updated analyses provided by the company, the ERG still considers Approach 1 to be appropriate for decision making.

The ERG note that the company did not provide an updated base case and has provided results incorporating this update in Section 2.

4. REFERENCES

1. National Institute for Health and Care Excellence. Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer [TA557] 2019 [cited February 2019]. Available from: https://www.nice.org.uk/guidance/ta557/history.
2. Velcheti V, Chandwani S, Chen X, Pietanza MC, Piperdi B, Burke T. Outcomes of first-line pembrolizumab monotherapy for PD-L1-positive (TPS ≥50%) metastatic NSCLC at US oncology practices. Immunotherapy. 2019;11(18):1541-54.