NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]

The final scope and final matrix are available on the NICE website

The following documents are made available to the consultees and commentators:

1. **Company submission from** Merck Sharp & Dohme UK

2. **Response to the clarification letters**
   - Company response to NICE's request for clarification
   - Company response to NICE's additional request for clarification

3. **Patient group, professional group and NHS organisation submission** from:
   - Roy Castle Lung Cancer Foundation
   - British Thoracic Oncology Group, National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians and Royal College of Radiologists
   - National Cancer Research Institute and British Thoracic Oncology Group

4. **Expert personal perspectives** from:
   - Alistair Greystoke – clinical expert, nominated by Merck Sharp & Dohme UK
   - Peter Clark – CDF clinical lead, NHS England

5. **Evidence Review Group report** prepared by School of Health and Related Research (ScHARR)

6. **Evidence Review Group report – factual accuracy check**

7. **Evidence Review Group report erratum - updated subsequent treatments proportion based on CDF clinical lead statement**

8. **Technical Report**

9. **Technical engagement response** from Merck Sharp & Dohme UK
   - Company response
   - Company response - supporting evidence

There were no comments received from the other stakeholders at the technical engagement stage.

10. **Technical engagement response from** experts**:**
    - NICE clinical questions sent to experts
    - Alistair Greystoke - clinical expert, nominated by Merck Sharp & Dohme UK Ltd response
    - [redacted] - clinical expert, nominated by British Thoracic Oncology Group (BTOG) response
    - NICE clarification questions to Alistair Greystoke
    - Alistair Greystoke response to NICE clarification questions

11. Evidence Review Group critique of company response to technical engagement prepared by School of Health and Related Research (ScHARR)

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated squamous non-small-cell lung cancer [ID1306]

Document B

Merck Sharp & Dohme

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Introduction to this document

This document represents the MSD UK evidence submission for the review of ID1306: Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated non-small-cell lung cancer.

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Abbreviations

AE – adverse events

AEOSI – adverse events of special interest

ALK – anaplastic lymphoma kinase

ASaT – all-patients-as-treated

BICR – blinded independent central review

CI – confidence interval

CR – complete response

CSR – clinical study report

DOR – duration of response

ECOG – Eastern cooperative oncology group

EGFR – epidermal growth factor receptor

EQ-5D – EuroQol 5 Dimension

HR – hazard ratio

HRQoL – health-related quality of life

ITT – intention-to-treat

IV – intravenous

KM – Kaplan-Meier

MA – marketing authorisation

NSCLC – non-small cell lung cancer

ORR – objective response rate

OD – overall survival

PD – progressive disease

PD-1 – programmed cell death 1 (receptor)

PD-L1 – programmed cell death 1 ligand 1

PD-L2 – programmed cell death 1 ligand 2

PFS – progression-free survival

PR – partial response

PRO – patient-reported outcome

Q3W – every 3 weeks

QoL – quality of life

RECIST 1.1 – response evaluation criteria on solid tumours, version 1.1

RCT – randomised controlled trial

SAE – serious adverse event

SD – standard deviation

SLR – systematic literature review

TPS – tumour proportion score

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

B.1.1 Decision problem

Details of the decision problem are presented in Table 1. The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE[1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated metastatic squamous non-small-cell lung cancer (NSCLC)	Adults with untreated metastatic squamous NSCLC	In line with the licence, based on the data from the supporting clinical trial KEYNOTE-407
Intervention	Pembrolizumab in combination with: • carboplatin and paclitaxel • carboplatin and nab-paclitaxel	Pembrolizumab in combination with • carboplatin and paclitaxel • carboplatin and nab-paclitaxel	In line with the licence
Comparator(s)	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab monotherapy (for people with tumours that express PD-L1 with at least 50% tumour proportion score with no EGFR- or ALK positive tumour mutations only)	As per final scope issued by NICE	Data from KEYNOTE-407 will provide comparative efficacy of pembrolizumab in combination with paclitaxel/nab-paclitaxel plus carboplatin. Data for comparative efficacy of pembrolizumab in combination with paclitaxel/nab-paclitaxel plus carboplatin versus remaining comparators will be derived from indirect treatment comparison (ITC).
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival	As per final scope issued by NICE	

	• response rates • duration of response • adverse effects of treatment • health-related quality of life.		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial access agreements for the intervention or	As per final scope issued by NICE	

	comparator technologies will be taken into account. If appropriate, the economic modelling should include the costs associated with diagnostic testing for biological markers (for example PD-L1) in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.		
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on the biological marker (PD-L1).	The following PD-L1 subgroups have been considered: • TPS <1%, ≥1%, 1-49%, ≥50%	

B.1.2 Description of the technology being appraised

The technology being appraised is pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel (referred to henceforth as pembrolizumab combination), as described in Table 3 below:

Table 2: Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab is a humanised monoclonal antibody which binds to the 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
Marketing authorisation/CE mark status	Pembrolizumab was granted marketing authorisation in May 2015 by the European Medicines Agency, covering all European Markets including the UK.[2]
Indications and any restriction(s) as described in the summary of product characteristics	Pembrolizumab (KEYTRUDA®) currently has a marketing authorisation (MA) covering the following indications as per the SmPC[2]: ▪ KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. ▪ 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 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. ▪ 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 (see section 5.1). ▪ 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 (see section 5.1). ▪ 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 (see section 5.1).
Method of administration and dosage	The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity.
Additional tests or investigations	Testing for PD-L1 tumour expression using a validated test is recommended for patients with NSCLC.[2] PD-L1 testing is an immunohistochemistry (IHC) test. IHC is part of routine pathology practice. MSD has supported the development of PD-L1 testing reference centres, which provide the capacity to enable the tumours from patients with advanced NSCLC to be tested for PD-L1 status. After the NICE recommendations for use of pembrolizumab for patients with advanced NSCLC in both first and second line, PD-L1 testing of all patients with advanced NSCLC has become part of routine clinical practice and PD-L1 testing has been added to the current panel of EGFR and ALK tests for NSCLC. [3]
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100 mg vial. [redacted]) Based on KEYNOTE-407 trial, the average time on therapy per patient is 191.4. days, equivalent to [redacted] cycles received per patient treated with

	pembrolizumab combination during a course of treatment. [4] The average cost per treatment course of pembrolizumab is [redacted] list price
Patient access scheme (if applicable)	[redacted]

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

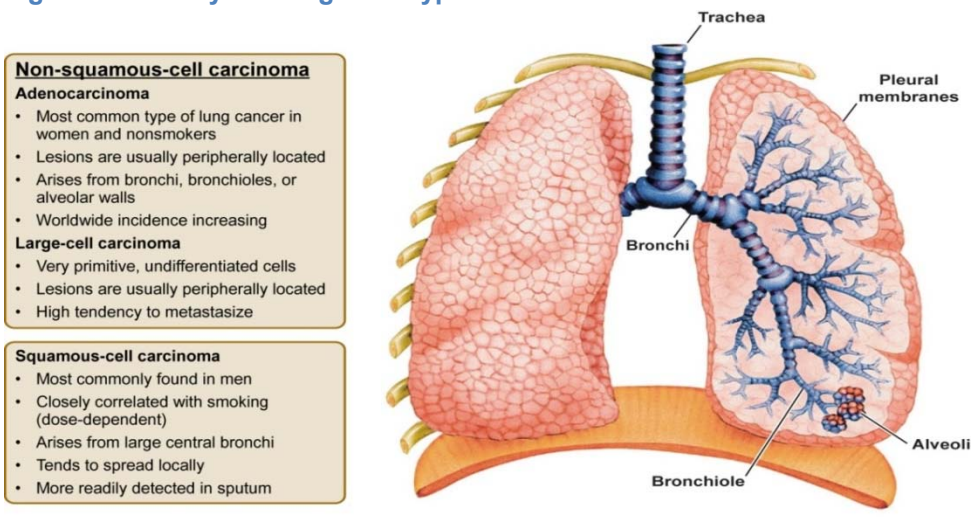
B.1.3.1 Lung cancer: an overview

Disease subtypes and classification

The term *lung cancer* is used for tumours arising from the respiratory epithelium (bronchi, bronchioles, and alveoli). According to the World Health Organization classification, epithelial lung cancers consist of two major cell types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[5]

NSCLC accounts for up to 85-90% of lung cancer cases in the UK[6] and includes two major histological subtypes: squamous cell carcinoma (25% to 30%) and non-squamous cell carcinoma, including adenocarcinoma (30% to 40%), large-cell carcinoma (10% to 15%), and other cell types (5%).[7, 8] The histological subtype of NSCLC correlates generally with the cancer's site of origin, reflecting the variation in respiratory tract epithelia (Figure 1). Adenocarcinoma is the most common form of NSCLC in many countries. It develops from mucus making cells in the lining of the airways and lesions are usually peripherally located. Squamous cell (epidermoid) carcinomas start in early version of squamous cells which are flat cells that line the inside of the airways in the lungs. They are often linked to a history of smoking and tend to be found in the central part of the lungs, near a main airway (bronchus)[7]. As squamous NSCLC is usually centrally located, typically arising in the proximal bronchi, it is more likely to invade larger blood vessels.

Figure 1: Primary histologic subtypes of NSCLC



NSCLC=non-small cell lung cancer. Source: Adapted from Teaching Times, 2016[9].

NSCLC is staged according to the Tumour-Node-Metastasis (TNM) classification, based on the primary tumour size and extent (T), regional lymph node involvement (N), and presence or absence of distant metastases (M).[10] This information is combined to assign an overall stage of 0, I, II, III, or IV as defined below:

- Stage 0: the cancer is found only in the top layers of cells lining the air passages
- Stages I and II: an invasive cancer has formed but has not spread to lymph nodes or distant sites
- Stage III: the cancer has spread to lymph nodes in the middle of the chest, also described as locally advanced disease. Stage III has two subtypes:
    - Stage IIIA: the cancer has spread only to lymph nodes on the same side of the chest where the cancer started
    - Stage IIIB: the cancer has spread to the lymph nodes on the opposite side of the chest, or above the collar bone.
- Stage IV: the cancer has spread to distant lymph nodes or to other organs such as the liver, bone, or brain.

Molecular biomarkers

Lung cancer cells harbour multiple chromosomal abnormalities, including mutations, amplifications, insertions, deletions, and translocations.[5, 8, 11] Molecular aberrations in genes encoding signalling proteins that drive initiation and maintenance of tumour cells are important markers of prognosis and response to treatment. The discovery of recurrent mutations in the Epidermal Growth Factor Receptor (EGFR) kinase as well as fusions involving the Anaplastic Lymphoma Kinase (ALK), has led to a dramatic change in the treatment of patients with lung adenocarcinoma, the most common type of lung cancer[12]. However, activating mutations in *EGFR* and *ALK* fusions are typically not present in lung squamous cell carcinoma, and targeted agents developed for lung adenocarcinoma are largely ineffective against this histology subtype.[12]

As research continues, more biomarkers are being discovered. Programmed cell death ligand 1 (PD-L1), the ligand of PD-1 receptor, is a cell surface protein that has recently been studied in a number of resected NSCLC specimens; pembrolizumab studies have shown

that the percentage of patients with advanced NSCLC whose tumours express PD-L1 is between 60% and 66%.[13-15] Treatment options for patients with squamous and non-squamous NSCLC were improved with approval of pembrolizumab as monotherapy in treatment-naïve patients with metastatic NSCLC with high PD-L1 expression (TPS ≥50%) without targetable EGFR or ALK genetic aberrations, however, only 25% to 30% of treatment-naive patients with squamous NSCLC are eligible for pembrolizumab monotherapy.[13, Herbst, 2015 #108]The recommendations for the rest of the squamous NSCLC patients -which is the vast majority- is the same as a decade ago highlighting the unmet need of the disease.

Incidence and prevalence

Lung cancer is the third most common cancer for both males and females in England. In 2016, there were a total of 38,370 newly diagnosed cases registered in England (ICD-10: C33-C34)[16], accounting for 13% of the total cancer registrations[17]. Almost 88.5% of the registered lung cancer cases in 2016 were NSCLC out of which 22% had a histology that it was of squamous origin[18]. An estimated 57,200 people who had previously been diagnosed with lung cancer were alive in the UK at the end of 2010[17].

The age-standardised rate for lung cancer has decreased in males from 127.9 in 1995 to 89.8 cases per 100,000 males in 2016, whilst female age-standardised rates for lung cancer have increased in this same period, from 51.4 in 1995 to 65.5 cases per 100,000 females in 2016[16]. Although the age-specific incidence of lung cancer is falling nationally as smoking prevalence falls, there has been a steady rise in the total number of lung cancer patients, partly owing to the ageing population.[19]

Diagnosis, treatment and prognosis

Diagnosis of lung cancer is based on physical examination, symptoms, smoking history and standard tests including blood tests and imaging analyses. Where lung cancer is diagnosed, pathological diagnosis of tissue biopsies is conducted to provide details of cancer subtype, disease staging and molecular markers.[20]

Squamous cell lung cancer is challenging to treat as a result of specific patient and disease characteristics, including older age and advanced disease at diagnosis, a higher incidence of comorbidities such as chronic obstructive pulmonary disease and heart disease compared with in non-squamous NSCLC.[21] Squamous NSCLC is usually centrally located, typically

arising in the proximal bronchi, and as a consequence, it is more likely to invade larger blood vessels. Additionally, mutations/alterations for which targeted treatments are approved are rare in squamous NSCLC.[21]

While NSCLC is potentially curable with surgery when diagnosed at an early stage, the majority of patients are diagnosed at an advanced stage of disease (stages IIIB-IV) when curative surgical treatment is no longer viable and prognosis is poor.[22] In 2016, 49.7% of lung cancer patients in England were diagnosed with stage IV of the disease.[18] One of the reasons for delayed diagnosis is that the most common symptoms of NSCLC (e.g. cough, shortness of breath and chest pain) are similar to those associated with conditions such as smoking and chronic bronchitis, making early diagnosis extremely difficult. The majority of lung cancer cases (85.6%) occur as a result of tobacco smoking (including environmental smoke exposure) and progress in smoking cessation is now reflected in declining lung cancer rates and mortality[23]. Active tobacco smoking has a stronger association with squamous disease than with adenocarcinoma.[21]

Treatment for patients with advanced NSCLC aims to prolong OS and improve HRQoL by improving symptoms. The clinical care pathway for patients with advanced squamous NSCLC is determined by the tumour histological subtype, the molecular biomarkers present and the performance status of the patient. Section B.1.3.2 provides details of the clinical pathway of care for advanced squamous NSCLC patients in the UK.

In the UK, lung cancer is the most common cause of cancer death. Approximately 35,620 people died from lung cancer in the UK, accounting for 21% of all cancer deaths in 2016.[24] Based on 2010-2011 data, approximately 10% of lung cancer patients (across all stages of disease) in England and Wales survive for five years or more post diagnosis. Only 5% of lung cancer patients survive for 10 years or more post diagnosis.[6]

Survival is strongly related to the stage of disease at diagnosis. The most recent UK data from the National Cancer Registration and Analysis Service – Public Health England (based on diagnoses from 2012 to 2014) indicate one-year survival of 15% for men and 19% for women diagnosed with Stage IV lung cancer.[25] In an analysis of 2006-2011 data from the UK National Lung Cancer Audit, 5-year survival of patients diagnosed at stage IV was reported at only 3%.[26] However with the changing landscape of metastatic NSCLC with immune oncology therapy (IO) being available at first and second lines of treatment, the true value of 5 year survival is uncertain with accepted estimates from a recent NICE TA being

around 10% in 1L squamous and non-squamous combined NSCLC population expressing TPS >50%[27].

The number of expected cases of squamous NSCLC for 2019 in England is 7,561; of which 3,759 are expected to be stage IV. In total, 2,025 of these patients are expected to be eligible for treatment with pembrolizumab in combination with chemotherapy (Table 3). (See Budget Impact Model Document for additional details).

Table 3: Estimated patient numbers for England, 2019-2023

	2019	2020	2021	2022	2023
Cases of lung cancer in England	38,832	38,988	39,144	39,300	39,457
Cases of confirmed NSCLC over total lung cancer	34,367	34,504	34,642	34,781	34,920
Cases of confirmed squamous NSCLC over total lung cancer	7,561	7,591	7,621	7,652	7,682
Estimated number of incident squamous NSCLC patients stage IV	3,759	3,774	3,789	3,805	3,820
Estimated number of NSCLC patients stage IV to be treated that are PS 0-1	2,025	2,033	2,042	2,050	2,058
Total patients eligible for pembrolizumab in combination	2,025	2,033	2,042	2,050	2,058

*PS: Performance Status based on Eastern Cooperative Oncology Group (ECOG) performance status scale

B.1.3.2 UK clinical care pathway

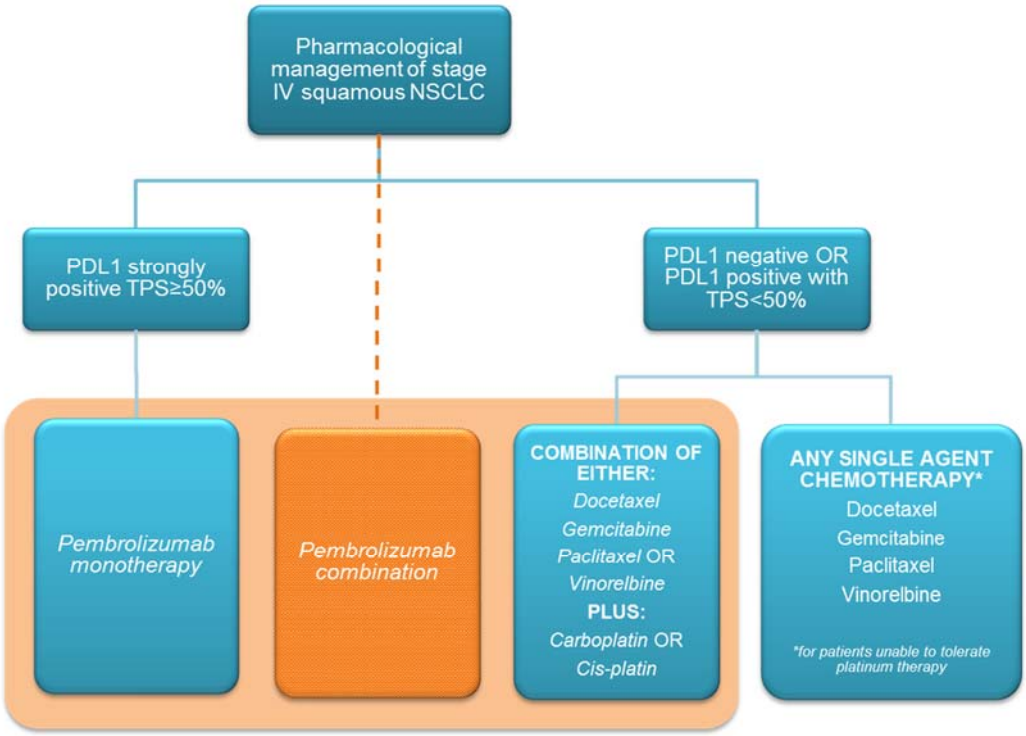
The clinical care pathway for patients with advanced NSCLC is determined by the tumour histological subtype, genotype, and the performance status of the patient and therapy aims to improve survival, disease control and quality of life. Due to the characteristics of the squamous histologic type many of the several recent treatments for NSCLC, including novel drugs targeting oncogenic drivers, new chemotherapeutic agents, and antiangiogenic therapies, have all demonstrated limitations in terms of efficacy and/or safety in squamous NSCLC.[28] Therefore, the recommendations for first-line treatment in the vast majority of patients with squamous NSCLC are the same as a decade ago (i.e., platinum-doublet chemotherapy)[28]

According to current NICE guidance, for patients with NSCLC with good performance status (WHO 0, 1 or a Karnofsky score of 80–100), chemotherapy is recommended as a treatment

option; where the chemotherapy should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) (NICE CG121)[29], see Figure 1. Patients who are unable to tolerate such combination may be offered single-agent chemotherapy with a third-generation drug[29], see Figure 1. Pembrolizumab monotherapy is also recommended in routine commissioning for patients with tumours expressing PD-L1 with at least a 50% tumour proportion score (TPS) (TA531)[27] see Figure 1. Since PD-L1 test requisition has become incorporated into hospital treatment pathways and protocols, there has been a significant increase in the volume of PD-PD-L1 testing across the UK.

Figure 2 shows the position within the care pathway which pembrolizumab combination therapy is expected to be placed at and offer patients who have advanced/metastatic, squamous NSCLC, and a performance status of 0-1 another option for treatment.

Figure 2.Treatment flow diagram for first line treatment of patients with advanced squamous NSCLC



Details of other clinical guidelines and national policies are summarised below:

European Society for Medical Oncology (ESMO)[30]

ESMO last published clinical practice guidelines concerning the diagnosis, treatment and follow-up of metastatic NSCLC in 2016. The landscape of NSCLC has changed significantly since then, with immunotherapies now being considered standard of care in a number of sub-populations of the disease.

For squamous NSCLC patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2, the recommended first-line treatment option is platinum-based doublet chemotherapy with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes)[30]. Single-agent chemotherapy with gemcitabine, vinorelbine and docetaxel represents an alternative treatment option.

For patients (<70 years old) with ECOG PS 0-1, apart from platinum doublets (Cisplatin with either gemcitabine, docetaxel or vinorelbine; carboplatin with either paclitaxel or nab-paclitaxel), options include the combination of Cisplatin/gemcitabine/necitumumab (if EGFR expression by ImmuniHistoChemistry –IHC).

In patients who were never smokers and are positive to molecular test for EGFR and ALK mutations, targeted therapy should be considered as first line treatment.

National Comprehensive Cancer Network (NCCN) (2017)[31]

The recently updated NCCN guideline (version 6.2017) states that for patients with metastatic NSCLC who test positive for PD-L1 expression (≥50%) and who are EGFR, ALK and ROS1 negative or unknown, first line therapy with pembrolizumab is recommended (category 1). The guideline recommends IHC testing for PD-L1 expression (category 2A) before first-line treatment to assess whether patients are candidates for pembrolizumab.

For squamous NSCLC patients not meeting the above criteria the NCCN guideline recommends initial cytotoxic therapy (first-line treatment) with platinum based chemotherapy if ECOG performance status (ECOG PS) 0 – 2. Doublet chemotherapy regimen is preferred however; patients may be eligible only for a single-agent therapy. The initial cytotoxic therapy options for squamous cell carcinoma (PS 0-1) are: Carboplatin/albumin-bound paclitaxel, Carboplatin/docetaxel, Carboplatin/gemcitabine, Carboplatin/paclitaxel, Cisplatin/docetaxel, Cisplatin/etoposide, Cisplatin/gemcitabine, Cisplatin/paclitaxel, Gemcitabine/docetaxel, Gemcitabine/Vinorelbine

Also, for the 2018 update (version 5) the NCCN Panel added a fist-line therapy recommendation for carboplatin/paclitaxel (or nab-paclitaxel)/pembrolizumab for patients with metastatic squamous NSCLC based on preliminary data from phase 3 trial KEYNOTE 407. For the update of version 6 in 2018, the Panel clarified that nab-paclitaxel can be substituted for paclitaxel. This pembrolizumab/chemotherapy regimen is recommended for patients whose PD-L1 levels are less than 50% or unknown. Maintenance therapy with pembrolizumab is also a recommended option.

B.1.4 Equality considerations

We do not envisage any equity or equality issues with the use of pembrolizumab combination in the treatment of adults with untreated metastatic squamous NSCLC.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D1.1 for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

A systematic literature review (SLR) was conducted to identify all relevant published and unpublished randomised control trials (RCTs) relating to pembrolizumab in combination with chemotherapy and relevant comparators as per the final scope described in Table 1. As the manufacturer of pembrolizumab, MSD is aware of all relevant clinical trials for pembrolizumab in combination with chemotherapy in this indication.

The full SLR methodology and results are presented in Appendix D1.1. The SLR yielded a total of 58 publications pertaining to 36 relevant RCTs were identified: 35 trials reporting comparators included in the decision problem (including 2 trials relating to pembrolizumab monotherapy; KEYNOTE-024[32, 33] and KEYNOTE-042[34] and 1 study reporting pembrolizumab in combination with chemotherapy in the squamous NSCLC population of interest (KEYNOTE-407).[4, 35]

The clinical effectiveness evidence presented in this submission is focused on the KEYNOTE-407 trial, the pivotal phase III RCT assessing the safety and efficacy of pembrolizumab in combination with chemotherapy compared with saline placebo plus chemotherapy, in patients with previously untreated metastatic squamous NSCLC (see Table 4).[4, 35] While KEYNOTE-407 is ongoing, data from the second interim analysis (IA2; data cut-off date 03-APR-2018) form the evidence base for this submission as described through Sections B2.2 to B2.6. In addition, these study data form the clinical evidence base included in the cost-effectiveness model and analyses presented in Section B.3. The final analysis of KEYNOTE-407 is currently anticipated in [redacted]

KEYNOTE-407 safety and efficacy data form the basis of the regulatory application to the European Medicines Agency (EMA) for marketing authorisation of pembrolizumab combination in patients with previously untreated metastatic squamous NSCLC.

Table 4: Clinical Effectiveness Evidence – KEYNOTE-407[4]

Study	KEYNOTE-407; An ongoing, randomised, double-blind, phase III study of intravenous (IV) pembrolizumab combined with carboplatin-paclitaxel/nab-paclitaxel chemotherapy versus saline placebo combined with carboplatin-paclitaxel/nab-paclitaxel chemotherapy in subjects with metastatic squamous non-small cell lung cancer (NSCLC) who have not previously received systemic therapy for metastatic disease – data cut-off date 03-APR-2018; NCT02775435				
Study design	Randomised, multi-centre, double-blind, placebo-controlled with active treatment, parallel-group study				
Population	Patients with metastatic squamous NSCLC who had not previously received systemic therapy for advanced disease; an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1; no active, symptomatic, or clinically unstable central nervous system metastases; and a life expectancy of at least 3 months				
Intervention(s)	Pembrolizumab 200 mg plus investigator's choice of paclitaxel or nab-paclitaxel plus carboplatin for 4 cycles followed by pembrolizumab for up to 31 cycles (Note: During the initial 4 cycles of treatment, all drugs were administered on day 1 of each cycle; nab-paclitaxel was also administered on days 8 and 15 of each 3 week cycle)				
Comparator(s)	Saline placebo plus investigator's choice of paclitaxel or nab-paclitaxel plus carboplatin for 4 cycles followed by saline placebo for up to 31 cycles (Note: During the initial 4 cycles of treatment, all drugs were administered on day 1 of each cycle; nab-paclitaxel was also administered on days 8 and 15 of each 3 week cycle)				
Indicate if trial supports marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	KEYNOTE-407 is the pivotal trial in this indication				
Reported outcomes specified in the decision problem	**overall survival (OS)** **progression-free survival (PFS)** objective response rates (ORR) duration of response (DoR) **adverse effects (AEs) of treatment** **health-related quality of life (HRQoL)** *Bolded outcomes are those included in the health economic model*				
All other reported outcomes	N/A				

B.2.3 Summary of methodology of KEYNOTE-407

Trial design[4, 36]

KEYNOTE-407 is a Phase 3, worldwide, randomized, placebo controlled with active treatment, parallel group, multi-site, double blind study of pembrolizumab combined with carboplatin and paclitaxel (or nab-paclitaxel) versus saline placebo combined with carboplatin and paclitaxel (or nab-paclitaxel) in participants with untreated metastatic squamous NSCLC.

The total planned enrolment was 560 eligible patients; 559 patients were ultimately randomised 1:1 as indicated below:

- Arm 1 (N=278): pembrolizumab 200mg plus carboplatin AUC 6 plus investigator's choice of paclitaxel 200mg/m2 or nab-paclitaxel 100mg/ m2 given every 3 weeks (Q3W) for 4 cycles followed by pembrolizumab 200mg Q3W until progression.
- Arm 2 (N=281): saline placebo plus carboplatin AUC 6 plus investigator's choice of paclitaxel 200mg/m2 or nab-paclitaxel 100mg/ m2 every 3 weeks (Q3W) for 4 cycles followed by saline placebo Q3W until progression.

Study subjects were stratified by paclitaxel vs nab-paclitaxel, PD-L1 status (TPS ≥1% vs. <1%) and geographic region of enrolling site (East Asia vs. non-East Asia) prior to randomisation.

Treatment with pembrolizumab or saline placebo continued until 35 study treatments had been administered or subject withdrawal or discontinuation criteria were met as outlined below:

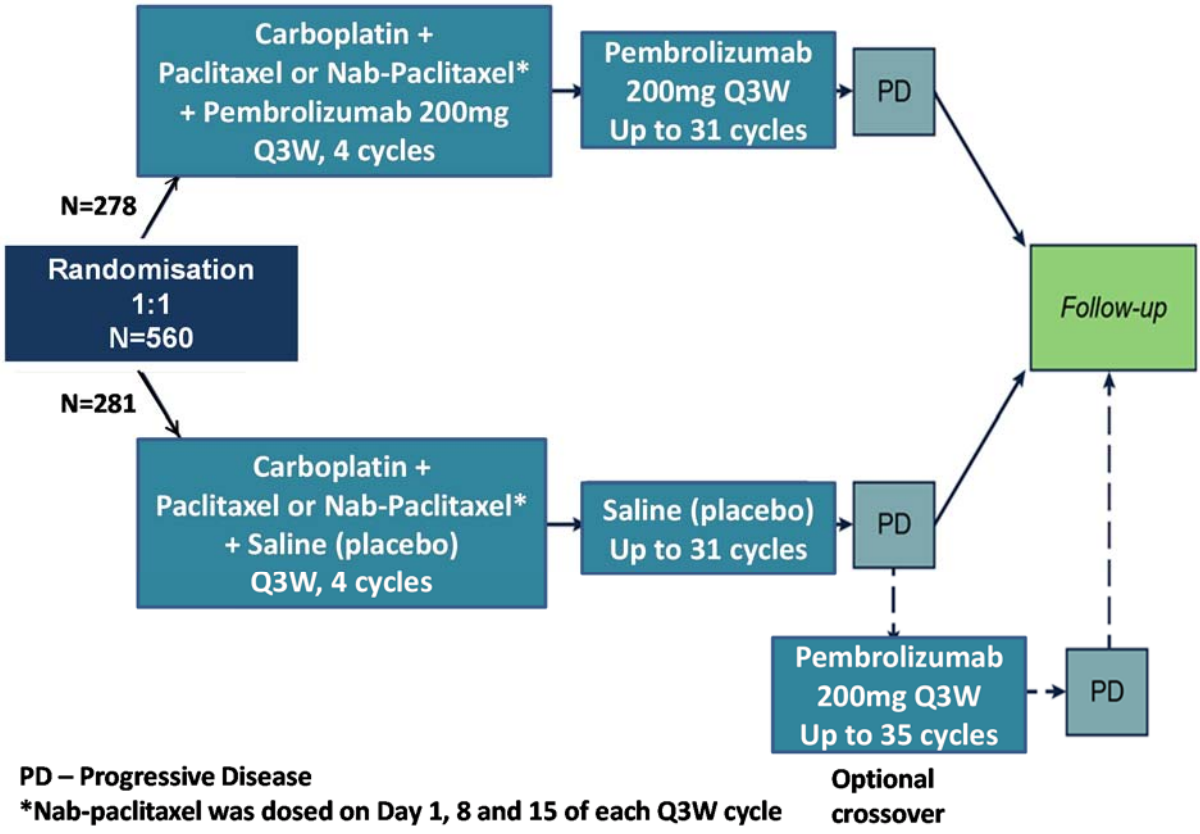
- Unacceptable adverse experiences
- Documented disease progression
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject from treatment
- Confirmed positive serum pregnancy test
- Noncompliance with trial treatment of procedure requirements
- Administrative reasons.

When a subject discontinued/withdrew from the study, all applicable activities scheduled for the end of treatment visit were performed at the time of discontinuation.

Following randomisation, patients' response to treatment was assessed using radiographic imaging at 6 and 12 weeks, followed by imaging every 9 weeks until week 48 and every 12 weeks for the remainder of the study. All imaging was submitted without indication of treatment assignment to a central vendor for blinded independent central review (BICR) of imaging using Response Evaluation Criteria In Solid Tumours 1.1 (RECIST 1.1) to determine PFS and ORR. Treatment decisions were made by investigators based on local radiological review based on immune-related RECIST (irRECIST) criteria and disease progression was verified by central radiological review. Adverse events (AEs) were monitored throughout the study and severity of AEs was graded according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

After documented disease progression based on BICR per RECIST 1.1, patients had their treatment unblinded and those in the control arm had the opportunity to receive pembrolizumab treatment in a Crossover Phase. Response or progression during the crossover phase was not considered for the analyses presented in this report. Figure 3 illustrates the KEYNOTE-407 study design.

Figure 3: KEYNOTE-407 study design



Source: Clinical Study Report[4]

Eligibility criteria[4, 36]

Male/female subjects with a diagnosis of squamous NSCLC who had not received prior systemic chemotherapy treatment for their metastatic NSCLC, who were at least 18 years of age, were eligible for enrolment in the trial. The key inclusion and exclusion criteria applied during the selection of the study population are presented in Table 5.

Table 5: Key inclusion and exclusion criteria

Inclusion criteria
• Histologically/cytologically confirmed diagnosis stage IV (M1a or M1b) squamous NSCLC. Patients with mixed histology (example adenosquamous) were allowed if there was squamous component in the specimen. • Measurable disease based on RECIST 1.1 as determined by local site investigator/radiology assessment • No prior systemic treatment for metastatic NSCLC at screening • Tumour tissue available from locations not radiated prior to biopsy • ≥18 years of age on day of signing informed consent • Life expectancy of at least 3 months • ECOG performance status 0 or 1 • Adequate organ function
Exclusion criteria
• Received prior systemic cytotoxic chemotherapy for metastatic disease; received other targeted or biological antineoplastic therapy before the first dose of study treatment; had major surgery within 3 weeks prior to first dose • Received radiation therapy to the lung that is >30Gy within 6 months of first dose • Completed palliative radiotherapy within 7 days of first dose • Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases and patients with untreated, asymptomatic brain metastases may participate if they met specific criteria • Pre-existing peripheral neuropathy that was ≥Grade 2 by CTCAE version 4 criteria • Active autoimmune disease that required systemic treatment in past 2 years • Taking chronic systemic steroids • Unable or unwilling to take folic acid or vitamin B12 supplementation • Prior treatment targeting PD-1, PD-L1/PD-L2, or other immune-regulatory receptors or mechanisms • Active infection requiring therapy • Interistitial lung disease or history of pneumonitis that required oral or intravenous glucocorticoids to assist with management.

Source: Clinical Study Report[4]

Settings and locations where the data were collected[4, 35, 36]

The study was conducted at 137 centres in 17 countries in North America, Europe, the Middle East, Asia and Australia. All treatments were administered in secondary care centres on an out-patient basis.

Trial drugs and concomitant drugs[4, 36]

Details of the trial drugs are presented in Table 6.

Table 6: Study treatments

Drug	Dose/ Potency	Dose Frequency	Route of administration	Regimen/ treatment period	Use
Pembrolizumab[1]	200mg	Q3W	IV infusion	Day 1 of each 21-day cycle for up to 35 cycles	Experimental
Normal saline[1]	N/A	Q3W	IV infusion	Day 1 of each 21-day cycle for up to 35 cycles	Placebo
Paclitaxel[2]	200mg/m^2	Q3W	IV infusion	Day 1 of each 21-day cycle for 4 cycles	Active comparator
Nab-paclitaxel[2]	100mg/m^2	Q1W	IV infusion	Day 1, 8 and 15 of each 21-day cycle for 4 cycles	Active comparator
Carboplatin[3]	AUC 6 mg/mL/min	Q3W	IV infusion	Day 1 of each 21-day cycle for 4 cycles	Active comparator

[1]Pembrolizumab/Normal Saline to be administered prior to chemotherapy.
[2]Investigator's choice of either paclitaxel or nab paclitaxel.
[3]Carboplatin dose should not to exceed 900mg.

Source: Clinical study report[4]

All treatments that the investigator considered necessary for a patient's welfare, including palliative and supportive care, could be administered at the discretion of the investigator in-keeping with the community standards of medical care. All concomitant medication used from 30 days before the first dose of study treatment through the Safety Follow-up Visit was recorded on the case report form (CRF), including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. After the Safety Follow-up Visit, only medications taken for serious adverse events (SAEs) and events of clinical interest (ECIs) were recorded.

Patients were prohibited from receiving chemotherapy and biologic or immuno- therapy not specified in the protocol, radiation, other investigational agents, live vaccines and systemic glucocorticoids (for any purpose other than to modulate symptoms from an immune-related AE) during the Screening, Treatment, Crossover, and Second Course Phases of this study. There were no prohibited therapies during the Post-Treatment Follow-Up Phase.

Study blinding/masking[36]

The study was double-blinded, with the patient, investigator and Sponsor personnel or delegates unware of treatment group assignments. The clinical supplies were provided open-label and an unblinded pharmacist provided the investigative staff with ready-to-use blinded pembrolizumab or saline infusion solutions, packaged identically in order to maintain the blinding, for administration at scheduled infusion visits.

Treatment identification information was unmasked only if necessary for the welfare of the subject. Once an emergency unblinding occurred, the principal investigator, site personnel, and Sponsor personnel were unblinded so that appropriate follow-up medical care could be provided to the subject.

Outcomes used in the economic model

The outcomes of overall survival (OS), progression free survival (PFS), and patient HRQoL were included within the health economic model, along with details of time on treatment (ToT) and adverse events (AEs), as reported in Section B.3. The OS and PFS outcomes were pre-specified as co-primary endpoints in KEYNOTE-407, while patient reported outcomes (PRO) as measured using the European Quality of Life Five Dimensions Questionnaire (EQ-5D), was pre-specified as an exploratory endpoint.

Objectives and hypotheses[36]

Full details of the objectives and hypotheses and the outcomes used in the KEYNOTE-407 study are presented below:

Primary objectives and hypotheses

In 1L subjects with metastatic squamous non-small cell lung cancer (NSCLC) receiving investigator's choice of standard of care chemotherapy (i.e. carboplatin and a taxane):

1. Objective: Evaluate progression free survival (PFS) per RECIST 1.1 as assessed by a central imaging vendor in subjects treated with Pembrolizumab compared to placebo.

   Hypothesis: Pembrolizumab prolongs PFS by RECIST 1.1 as assessed by a central imaging vendor compared to placebo.

2. Objective: Evaluate overall survival (OS) in subjects treated with Pembrolizumab compared to placebo.

   Hypothesis: Pembrolizumab prolongs OS compared to placebo.

Secondary objectives

In 1L subjects with metastatic squamous non-small cell lung cancer (NSCLC) receiving investigator's choice of standard of care chemotherapy (i.e. carboplatin and a taxane):

1. Objective: Evaluate the objective response rate (ORR) and duration of response (DOR) per RECIST 1.1 as assessed by a central imaging vendor in subjects treated with Pembrolizumab compared to placebo.

   Hypothesis: Pembrolizumab improves ORR per RECIST 1.1 as assessed by a central imaging vendor compared to placebo

2. Objective: Evaluate the safety and tolerability profile of Pembrolizumab.

Key exploratory objectives

1. Objective: Evaluate the pembrolizumab combination compared with the control with respect to:
   a) PFS per RECIST 1.1, as assessed by investigator review in the next line of therapy (PFS2)
   b) PFS per irRECIST, as assessed by site investigator
   c) ORR and DOR per irRECIST, as assessed by site investigator
   d) PFS and ORR per RECIST 1.1 as assessed by central imaging vendor and OS by PD-L1 status (≥1% vs <1%) and by taxane (investigator's choice of paclitaxel or nab-paclitaxel)

2. To evaluate changes in health-related quality-of-life assessments from baseline in the overall study population and by PD-L1 expression level using the EORTC QLQ-C30 and EORTC QLQ-LC13.

3. To characterize utilities in participants treated with the pembrolizumab chemotherapy combination compared with the control using the EuroQoL(EQ)-5D.

Patient characteristics at baseline

Baseline characteristics of the patients in the Intention-to-treat (ITT) population in KEYNOTE-407 are presented in Table 7. As the table shows, in general, demographic and baseline characteristics were well-balanced between the pembrolizumab combination and the control groups.

Participants were enrolled regardless of PD-L1 status and were distributed within each of the three PD-L1 TPS subgroups as follows: approximately 35% in TPS <1%, 37% in TPS 1-49%, and 26% in TPS ≥50%, with comparable distributions between the pembrolizumab combination and the control. The distribution of tumour PD-L1 expression levels was consistent between the screened and randomized populations, and was similar to what has been reported in other KEYNOTE studies. The investigator's choice of taxane was paclitaxel in approximately 60% of participants in both treatment groups.

Concomitant medication use was generally consistent across treatment groups

The overall population and history of prior treatment are relevant to the UK and largely representative of UK clinical practice.

Table 7: Subject characteristics (ITT population)

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	278		281		559	
Gender						
Male	220	(79.1)	235	(83.6)	455	(81.4)
Female	58	(20.9)	46	(16.4)	104	(18.6)
Age (Years)						
< 65	127	(45.7)	127	(45.2)	254	(45.4)
>= 65	151	(54.3)	154	(54.8)	305	(54.6)
Mean	65.0		64.8		64.9	
SD	8.8		8.7		8.7	
Median	65.0		65.0		65.0	
Range	29 to 87		36 to 88		29 to 88	
Race						
American Indian Or Alaska Native	0	(0.0)	2	(0.7)	2	(0.4)
Asian	56	(20.1)	52	(18.5)	108	(19.3)

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Black Or African American	3	(1.1)	4	(1.4)	7	(1.3)
Native Hawaiian Or Other Pacific Islander	1	(0.4)	0	(0.0)	1	(0.2)
White	216	(77.7)	214	(76.2)	430	(76.9)
Missing	2	(0.7)	9	(3.2)	11	(2.0)
Ethnicity						
Hispanic Or Latino	31	(11.2)	24	(8.5)	55	(9.8)
Not Hispanic Or Latino	237	(85.3)	245	(87.2)	482	(86.2)
Not Reported	7	(2.5)	9	(3.2)	16	(2.9)
Unknown	3	(1.1)	3	(1.1)	6	(1.1)
Geographic Region						
US	13	(4.7)	22	(7.8)	35	(6.3)
Ex US	265	(95.3)	259	(92.2)	524	(93.7)
Geographic Region						
East-Asia	54	(19.4)	52	(18.5)	106	(19.0)
Non-East Asia	224	(80.6)	229	(81.5)	453	(81.0)
Geographic region						
EU	125	(45.0)	115	(40.9)	240	(42.9)
Non-EU	153	(55.0)	166	(59.1)	319	(57.1)
Smoking Status						
Never Smoker	22	(7.9)	19	(6.8)	41	(7.3)
Former Smoker	174	(62.6)	199	(70.8)	373	(66.7)
Current Smoker	82	(29.5)	63	(22.4)	145	(25.9)
ECOG						
0	73	(26.3)	90	(32.0)	163	(29.2)
1	205	(73.7)	191	(68.0)	396	(70.8)
Histology						
Squamous	272	(97.8)	274	(97.5)	546	(97.7)
Adenosquamous	6	(2.2)	7	(2.5)	13	(2.3)
Metastatic Stage						
M1A	111	(39.9)	107	(38.1)	218	(39.0)
M1B	167	(60.1)	174	(61.9)	341	(61.0)
Brain Metastasis Status at Baseline						
Yes	20	(7.2)	24	(8.5)	44	(7.9)
No	258	(92.8)	257	(91.5)	515	(92.1)
Baseline Tumor Size						
Subjects with data	273		279		552	
Mean	112.47		107.24		109.83	
SD	71.84		66.69		69.27	
Median	94.50		94.10		94.20	

	Pembrolizumab combination		Control		Total	
	n	(%)	n	(%)	n	(%)
Range	13.3 to 424.3		10.3 to 376.5		10.3 to 424.3	
PD-L1 Status (Cut Point: 1%)						
TPS < 1%	95	(34.2)	99	(35.2)	194	(34.7)
TPS >= 1%	176	(63.3)	177	(63.0)	353	(63.1)
Unknown	7	(2.5)	5	(1.8)	12	(2.1)
PD-L1 Status (Cut Point: 1% and 50%)						
TPS < 1%	95	(34.2)	99	(35.2)	194	(34.7)
TPS 1-49%	103	(37.1)	104	(37.0)	207	(37.0)
TPS >= 50%	73	(26.3)	73	(26.0)	146	(26.1)
Unknown	7	(2.5)	5	(1.8)	12	(2.1)
Taxane Chemotherapy						
+Paclitaxel	169	(60.8)	167	(59.4)	336	(60.1)
+Nab-Paclitaxel	109	(39.2)	114	(40.6)	223	(39.9)
Prior Adjuvant/Neo-adjuvant Therapy						
Yes	5	(1.8)	8	(2.8)	13	(2.3)
No	273	(98.2)	273	(97.2)	546	(97.7)
Prior Radiation						
Yes	35	(12.6)	38	(13.5)	73	(13.1)
No	243	(87.4)	243	(86.5)	486	(86.9)
Prior Thoracic Radiation						
Yes	17	(6.1)	22	(7.8)	39	(7.0)
No	261	(93.9)	259	(92.2)	520	(93.0)
Database Cut-off Date: 03APR2018						

Source: Clinical Study Report[4]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Key elements of the statistical analysis plan are summarised in Table 8.

The clinical evidence presented in this submission is based on IA2, which was to be performed after approximately 332 PFS events were observed. The overall type I error rate across multiple endpoints and time points was strictly controlled at α = 0.025 (one-sided) in this study using the graphical method of Maurer and Bretz [16.1.12.10]. According to this approach, ORR was tested in IA1 at one-sided 0.005 significance level. Since ORR was positive in IA1, the alpha from ORR was rolled over to PFS so that PFS was tested at a one-sided 0.015 significance level (across multiple analyses). Since

PFS was positive at IA2, the alpha from PFS was rolled over to OS so that OS was tested at an overall 0.025 significance level (across multiple analyses). A Lan-DeMets O'Brien-Fleming approximation spending function was used for the calculation of efficacy bounds for PFS and OS in IA2, based on the actual number of events observed for PFS (349 events) and OS (205 events).[36]

Table 8: Statistical analysis plan summary

Study design overview	Phase III study of pembrolizumab plus chemotherapy vs saline placebo plus chemotherapy in first line metastatic squamous NSCLC
Treatment assignment	Approximately 560 patients to be randomised 1:1 to receive pembrolizumab plus chemotherapy or saline placebo plus chemotherapy. Study is double-blinded
Analysis populations	Efficacy: Intention to treat (ITT) Safety: All patients as treated (ASaT)
Dual primary endpoints/ hypotheses	Hypothesis 1: Pembrolizumab plus chemotherapy combination prolongs PFS by RECIST 1.1 as assessed by BICR compared to saline placebo plus chemotherapy. Hypothesis 2: Pembrolizumab plus chemotherapy combination prolongs OS compared to saline placebo plus chemotherapy.
Statistical methods for key efficacy analyses	The dual primary hypotheses on PFS and OS evaluated by comparing pembrolizumab to saline placebo in combination with carboplatin and a taxane using a stratified Log-rank test. The hazard ratio estimated using a stratified Cox regression model. Event rates over time estimated within each treatment group using the Kaplan-Meier method. The stratified M&N method with sample size weights used for analysis of ORR.
Statistical Methods for Key Safety Analyses	Analysis of safety results follows a tiered approach; the tiers differ with respect to analyses performed. No Tier 1 safety parameters in the trial; all safety parameters considered either Tier 2 or Tier 3. Between-treatment differences in tier 2 parameters assessed in categories relevant to oncology studies, including selected AEs (≥10% incidence), selected Grade 3 to 5 AEs (≥1% incidence), and selected SAEs (≥1% incidence). Only point estimates by treatment group are provided for Tier 3 safety parameters. The between-treatment difference analysed using the Miettinen and Nurminen method. In primary safety comparison, patients who crossover to pembrolizumab censored at time of crossover (i.e., AEs occurring during treatment with pembrolizumab are excluded for control-arm patients). Exploratory safety analysis conducted for the crossover population, including all safety events starting from date of first dose of

	pembrolizumab.
Interim Analyses	Four analyses planned for the study: three interim analyses and one final analysis: Interim analysis 1: To demonstrate superiority of pembrolizumab in combination with carboplatin and a taxane in ORR; conducted after approximately 200 subjects have approximately 28 weeks of follow up Interim analysis 2: To demonstrate superiority of pembrolizumab in combination with carboplatin and a taxane in 1) PFS and 2) OS; to be performed after approximately 332 PFS events are observed Interim analysis 3: To demonstrate superiority of pembrolizumab in combination with carboplatin and a taxane in 1) PFS and 2) OS; to be performed after approximately 415 PFS events are observed.
Final Analysis	To demonstrate superiority of pembrolizumab in combination with carboplatin and a taxane in OS; to be performed after approximately 361 death events observed
Multiplicity	Graphical method of Maurer and Bretz to control multiplicity for multiple hypotheses as well as interim analyses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests. The overall type I error is controlled at 0.025 (one-sided) for the hypothesis testing of ORR, PFS and OS. The pre-allocated alpha is 0.005, 0.01 and 0.01 for ORR, PFS and OS, respectively. ORR may be tested at 0.005 or at 0.025 (if both PFS and OS are positive, using the p-value from IA1). PFS may be tested at 0.01 or at 0.015 (if ORR is positive but OS not positive), or at 0.02 (if OS is positive but ORR not positive) or at 0.025 (if both OS and ORR are positive). OS may be tested at 0.01 or at 0.02 (if PFS is positive but ORR not positive) or 0.025 (if both PFS and ORR are positive). A Lan-DeMets O'Brien-Fleming approximation spending function will be used for the calculation of efficacy bounds for PFS and OS.
Sample size and power	The final analysis occurs after ~361 deaths are observed unless the trial is terminated early. With 361 deaths, the study has ~92% power for detecting a hazard ratio (HR) of 0.7 at 0.025 (one-sided), ~90% power for detecting a HR of 0.7 at 0.02 (one-sided) and ~85% power for detecting a HR of 0.7 at 0.01 (one-sided). The planned sample size is approximately 560 subjects assuming ~15.5 months of enrolment.

Source: Clinical Study Protocol[36]; Clinical Study Report[4]

The strategy for analysis of key efficacy endpoints is summarised in Table 9, while Table 10 summarises the censoring rules applied for analyses of PFS.

Table 9: Analysis strategy for key efficacy endpoints

Endpoint	Statistical methods	Analysis population	Missing data approach
Primary endpoints			
PFS: Defined as time from randomisation to first documented disease progression per RECIST 1.1 based on blinded BICR or death due to any cause, whichever occurs first.	Non-parametric Kaplan-Meier method to estimate the PFS curves in each treatment group Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox proportional hazard model with Efron's tie handling method to assess the magnitude of treatment difference (i.e. hazard ratio)	ITT	Primary censoring rule Sensitivity analysis 1 Sensitivity analysis 2
OS: Defined as time from randomisation to death due to any cause.	Non-parametric Kaplan-Meier method to estimate the OS curves in each treatment group Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox proportional hazard model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Model based (censored at last known alive date)
Secondary endpoint			

ORR: Defined as the proportion of subjects who have a complete response (CR) or a partial response (PR) based on confirmed assessments by BICR per RECIST 1.1	Stratified Miettinen and Nurminen method with sample size weights	ITT	Patients without assessments are considered non-responders and conservatively included in denominator
DOR: Defined as time from first documented evidence of CR or PR until disease progression (by BICR per RECIST 1.1) or death	Descriptive statistics for range and Kaplan-Meier estimate of median	Patients in ITT population with an objective response	

Source: Clinical study protocol[36]

Table 10: Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death

Source: Clinical study protocol[36]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment of KEYNOTE-407 was conducted using the Cochrane Collaboration's Risk of Bias tool[37] and determined to be 'low risk.' The complete quality assessment is included in Appendix D. A tabulated summary of the quality assessment results is also presented in the table below.

Table 11: Quality assessment results for parallel group RCTs

Trial	KEYNOTE-407	Justification
Was randomisation carried out appropriately?	Yes	A computerized randomised list generator was utilized for sequence generation. Interactive voice response system (IVRS)/integrated web response system (IWRS) was used for randomisation
Was the concealment of treatment allocation adequate?	Yes	The Sponsor, investigator and subject were blinded to treatment allocation. The study site's unblinded pharmacist obtained each patient's study identification number and study drug assignment via the IVRS/IWRS and prepared the solutions for infusion. The unblinded pharmacist provided the investigative staff with ready-to-use blinded pembrolizumab/saline infusion solutions, packaged identically to maintain the blinding, for administration at scheduled infusion visits.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	In general, the treatment groups were relatively well balanced in terms of baseline characteristics.
Were care providers, patients and outcome assessors blind to treatment allocation?	Yes	The study was double-blind, with sponsor, investigator and subject blinded to treatment allocation. In addition, radiologists who assessed the tumour images were blinded.
Were there any unexpected imbalances in drop-outs between groups?	No	Discontinuations for reasons other than progressive disease or death were similar across both groups.

Trial	KEYNOTE-407	Justification
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Outcomes pre-specified in the study protocol were reported in trial results.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)		

Consideration of UK clinical practice

Currently in the UK, first-line treatment for the majority of patients with previously untreated metastatic squamous NSCLC is limited to chemotherapy.[29] Only those individuals whose tumour cells have high levels of PD-L1 expression (TPS score ≥50%) have routine access to innovative immuno-oncology treatment in the form of pembrolizumab monotherapy.[38] Data from KEYNOTE-407 show that pembrolizumab in combination with chemotherapy is a promising treatment option which has demonstrated efficacy, including survival benefits, in all squamous NSCLC patients regardless of PD-L1 expression, with an acceptable tolerability profile.[35]

KEYNOTE-407 recruited almost 43% of patients in Europe and baseline demographics suggest these patients were representative of those typically seen in UK clinical practice. While the control treatment in KEYOTE-407 was based on carboplatin plus either paclitaxel or nab-paclitaxel, in the UK cisplatin is more commonly used and nab-paclitaxel is not recommended for use in NSCLC patients. Analysis of the comparative efficacy of the current chemotherapy options indicates they each offer similar efficacy [39]. In addition, discussions with clinical experts in the UK have stated that the choice of carboplatin plus paclitaxel can be considered equal in outcomes to other chemotherapy regimens available in the UK. In contrast, the data from KEYNOTE-407 suggest that pembrolizumab in combination with chemotherapy could offer a significant step-change in benefit for these patients.

Considerable unmet need remains for additional treatments which provide survival benefits for those patients who are currently ineligible for first line immuno-oncology therapy who could realise greater survival benefits with pembrolizumab chemotherapy combination treatment.

B.2.6 Clinical effectiveness results of the relevant trials

The clinical data presented in this submission are from IA2 of the KEYNOTE-407 phase III trial of pembrolizumab plus chemotherapy combination versus saline placebo plus chemotherapy as first line treatment in patients with metastatic squamous NSCLC. [4, 35]

For simplicity, abbreviated nomenclature for the treatment groups is used in this section as per Table 12:

Table 12: Treatment group nomenclature

Treatment group	Abbreviated nomenclature
pembrolizumab/carboplatin/paclitaxel (or nab-paclitaxel)	pembrolizumab combination
carboplatin/paclitaxel (or nab-paclitaxel)	Control

The IA2 was performed on the primary (PFS and OS), secondary (ORR and DoR) and exploratory (PRO) efficacy endpoints, with a data cut-off date for the analysis of 3 April 2018. All efficacy analyses were conducted using the ITT population. At the IA2 data cut-off date, patients had a median duration of follow-up of 7.8 months (range 0.1 to 19.1), with 43.5% of patients in the pembrolizumab combination group and 25.7% in the control group remaining on assigned treatment. Mean duration of exposure was 191.4 days (SD 124.5 days) in the pembrolizumab combination arm compared with 143.7 days (SD 106.3 days) in the control arm. The mean number of cycles of treatment received was [redacted] (SD [redacted]) and [redacted] (SD [redacted]) in the pembrolizumab combination and control groups, respectively.[4, 35]

Table 13: Summary of drug exposure (ASaT population)

	Pembrolizumab combination (N=278)	Control (N=280)
Number of Days on Therapy		
Mean	191.4	143.7
Median	169	127
SD	124.5	106.3
Range	1 to 545	1 to 545
Number of Cycles		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Database Cut-off Date: 03APR2018		

Source: Clinical Study Report[4]

B.2.6.1 Summary of clinical efficacy outcomes (IA2)[4, 35]

A summary of the clinical efficacy outcome results from IA2 are presented in Table 14, with additional details of each endpoint provided in sub-sections B.2.6.2 to B.2.6.5.

Table 14: Summary of clinical efficacy outcomes (IA2)

	Treatment-naïve squamous NSCLC	
Number Patients	**Pembrolizumab combination N=278**	**Control N=281**
Primary endpoints		
OS - ITT population		
Median (95% CI), [months]	15.9 (13.2, -)	11.3 (9.5, 14.8)
	HR 0.64 (95% CI 0.49, 0.85); p=0.0008	
OS rate at 6 months	[redacted]	[redacted]
OS rate at 12 months	65.2%	48.3%
PFS (BICR per RECIST 1.1) – ITT population		
Median (95% CI), [months]	6.4 (6.2, 8.3)	4.8 (4.3, 5.7)
	HR 0.56 (95% CI 0.45, 0.70); p < 0.0001	
PFS rate at 6 months	[redacted]	[redacted]
PFS rate at 12 months	31.3%	14.4%
Secondary endpoints		
ORR (BICR per RECIST 1.1) - ITT Population		
Confirmed ORR%	57.9% (51.9, 63.8)	38.4% (32.7, 44.4)
Difference in % vs control	19.5% (11.2, 27.5); p<0.0001	
% of patients who achieved a CR	1.4%	2.1%
Disease control rate (CR+PR+SD)	86.0%	75.4%
Time to Response		
Number of responders (n) Median (range) [months]	161 1.4 (1.1-6.1)	108 1.4 (1.0-4.5)
Response Duration (BICR assessment) - ITT Population		
Median (range) [months]	7.7 (1.1+-14.7+)	4.8 (1.3+-15.8+)

Source: Clinical study report[4]; Paz-Ares 2018[35]

B.2.6.2 Overall survival[4, 35]

Overall survival (OS) is defined as time from randomisation to death due to any cause, expressed in days. Patients without documented death at the time of analysis were censored at date of last known contact. Patients who had survival update after the data cut-off date were censored at the cut-off date.

At the cut-off date, 205 deaths (38%) had been reported in the study; 85 (30.6%) in the pembrolizumab combination group and 120 (42.7%) in the control group.

Pembrolizumab combination provided clinically meaningful improvement in the OS of previously untreated participants with metastatic squamous NSCLC when compared with the control. The OS HR was 0.64 (95% CI: 0.49, 0.85; p=0.0008) in favour of the pembrolizumab combination, representing a 36% reduction in the risk of death. The median OS was longer in the pembrolizumab combination compared with the control (15.9 months vs 11.3 months).(Table 15) The OS rates at Month 6, Month 9, and Month 12 were all higher in the pembrolizumab combination compared with the control.(Table 16) The curves on the KM plot separated early and remained separated over time with the pembrolizumab combination demonstrating an improved OS.(Figure 4)

Table 15: Analysis of OS (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	vs. Control Hazard Ratio‡ (95% CI)‡ p-value‡‡
Pembrolizumab combination	278	85 (30.6)	2362.3	3.6	15.9 (13.2, .)	[redacted]	0.64 (0.49,0.85)
Control	281	120 (42.7)	2160.0	5.6	11.3 (9.5, 14.8)	[redacted]	0.0008

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cut-off Date: 03APR2018

Source: Clinical study report[4]; Paz-Ares 2018[35]

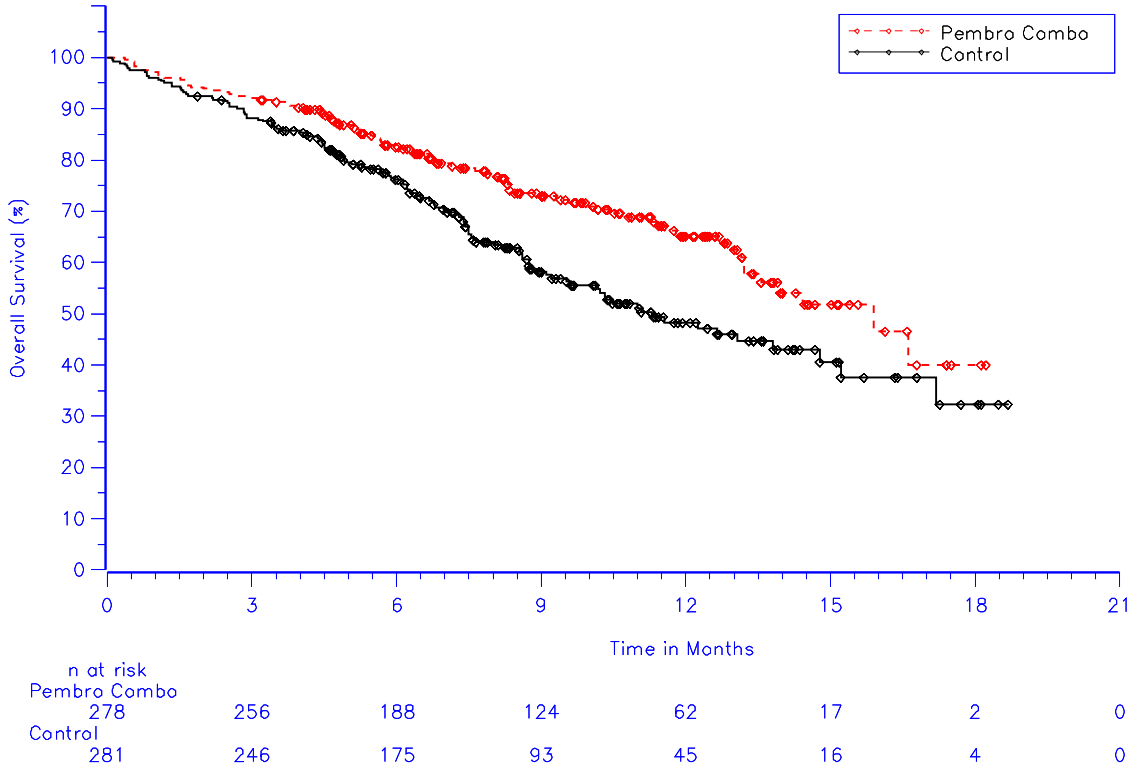
Table 16: Summary of OS rate over time (ITT population)

	Pembrolizumab combination (N=278) % (95% CI)†	Control (N=281) % (95% CI)†
Summary of Overall Survival rate at time point		
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	65.2 (57.7, 71.6)	48.3 (40.8, 55.4)

† From product-limit (Kaplan-Meier) method for censored data.
Database cut-off date: 03APR2018

Source: Clinical study report[4]

Figure 4: KM estimates of OS (ITT population)



Source: Clinical study report[4]

At the time of data cut-off, 72 of the 281 patients in the control ITT population were continuing the control treatment. Of the remaining 209 patients, 75 eligible patients with disease progression confirmed by BICR had crossed over to pembrolizumab monotherapy within the study and an additional 14 patients received a PD-1 antibody (pembrolizumab or nivolumab) as subsequent therapy outside of the study, resulting in an overall crossover rate

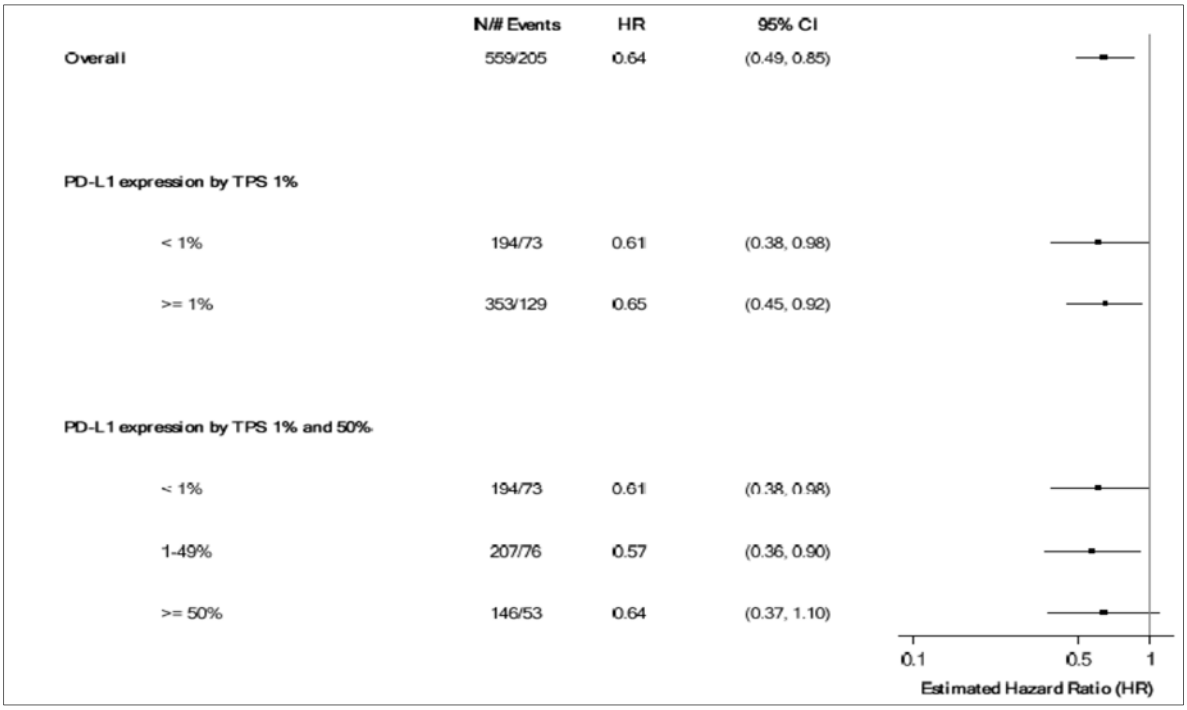
of 42.6% (89/209). Despite the high crossover rate from the control to an anti-PD-1 antibody, the OS benefit of the pembrolizumab combination treatment persisted.

OS by PD-L1 expression

The OS benefit of the pembrolizumab combination over the control was observed across all PD-L1 expression subgroups (TPS <1%, TPS 1-49%, and TPS ≥50%). An incremental OS benefit was observed with increased PD-L1 expression, with HRs of 0.61, 0.57 and 0.64 respectively. (Figure 5)

Median OS was longer in the pembrolizumab combination than control in each of the PD-L1 TPS <1% (15.9 vs 10.2 months) and TPS 1 to 49% (14.0 vs 11.6 months) subgroups. In the TPS ≥50% subgroup, the median OS was not reached in either the pembrolizumab combination or control groups. (Table 14)

Figure 5: Forest plot of OS hazard ratio by PD-L1 expression (ITT population)



Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. Non-East Asia).Subjects with PD-L1 not evaluable are not included in the subgroup analysis.
Database Cut-off Date: 03APR2018
Source: Clinical study report[4]; Paz-Ares 2018[35]

Table 17: Analyses of OS in PD-L1 subgroups (ITT population; TPS <1%, TPS 1-49%; TPS≥50%)

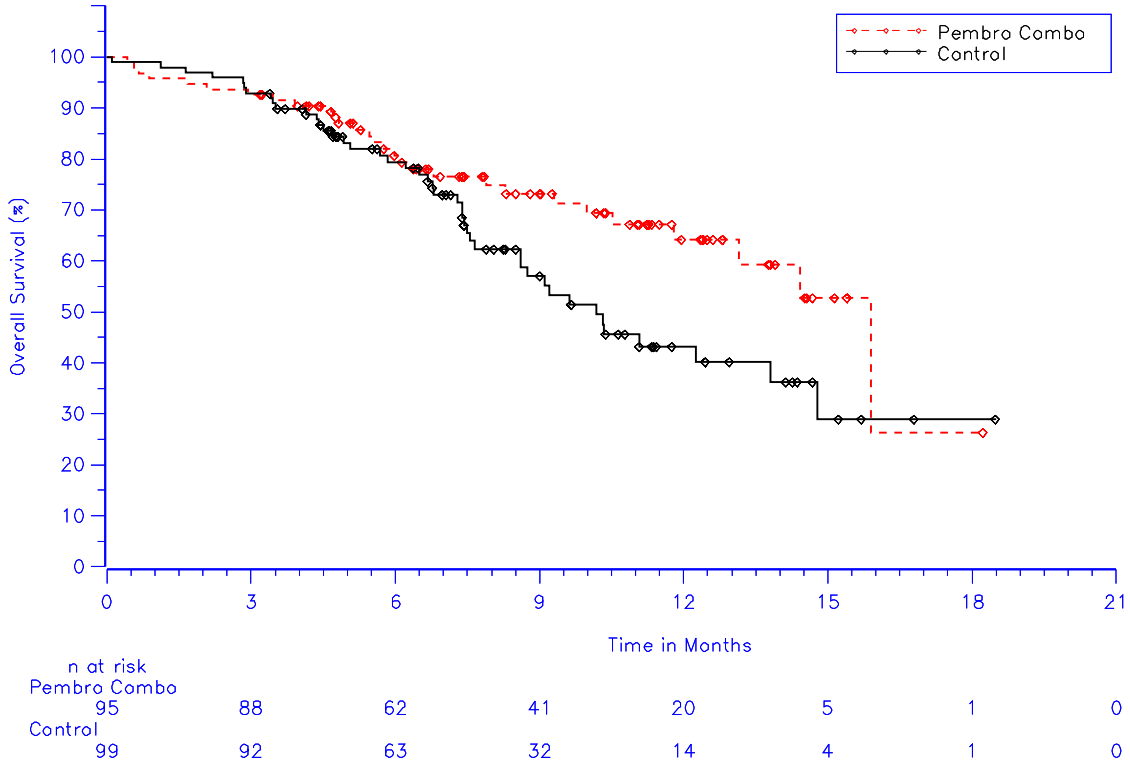
Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Month 6 in %† (95% CI)	vs. Control Hazard Ratio‡ (95% CI)‡ p-value‡‡
TPS<1%							
Pembrolizumab combination	95	29 (30.5)	788.4	3.7	15.9 (13.1, .)	80.7 (70.7, 87.5)	0.61 (0.38, 0.98) p=0.0188
Control	99	44 (44.4)	762.0	5.8	10.2 (8.6, 13.8)	79.4 (69.6, 86.4)	
TPS 1-49%							
Pembrolizumab combination	103	31 (30.1)	891.5	3.5	14.0 (12.8, .)	84.5 (75.6, 90.4)	0.57 (0.36, 0.90) p=0.0079
Control	104	45 (43.3)	811.6	5.5	11.6 (8.9, 17.2)	76.0 (66.3, 83.3)	
TPS≥50%							
Pembrolizumab combination	73	23 (31.5)	616.8	3.7	Not Reached (11.3, .)	81.9 (70.9, 89.1)	0.64 (0.37, 1.10) p=0.0523
Control	73	30 (41.1)	536.4	5.6	Not Reached (7.4, .)	71.3 (59.0, 80.5)	

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cut-off Date: 03APR2018

Source: Clinical study report[4]; Paz-Ares 2018[35]

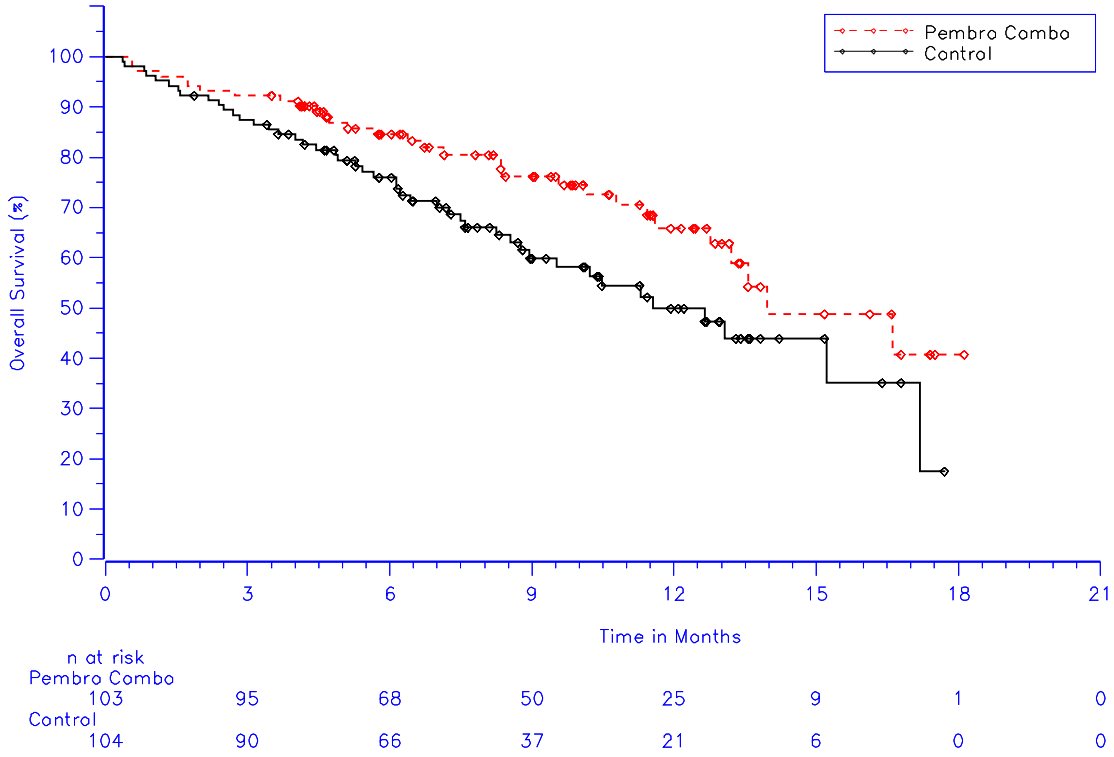
The KM curves for all PD-L1 subgroups demonstrated a consistent effect of pembrolizumab combination over control, regardless of PD-L1 expression status. The KM curves separated earlier as PD-L1 increased (after 7 months for TPS <1%, after 2 months for 1-49%, and at Month 0 for TPS ≥50%) and remained separated thereafter. (Figure 6, Figure 7, Figure 8.)

Figure 6: KM estimates of OS (ITT population; TPS<1%)



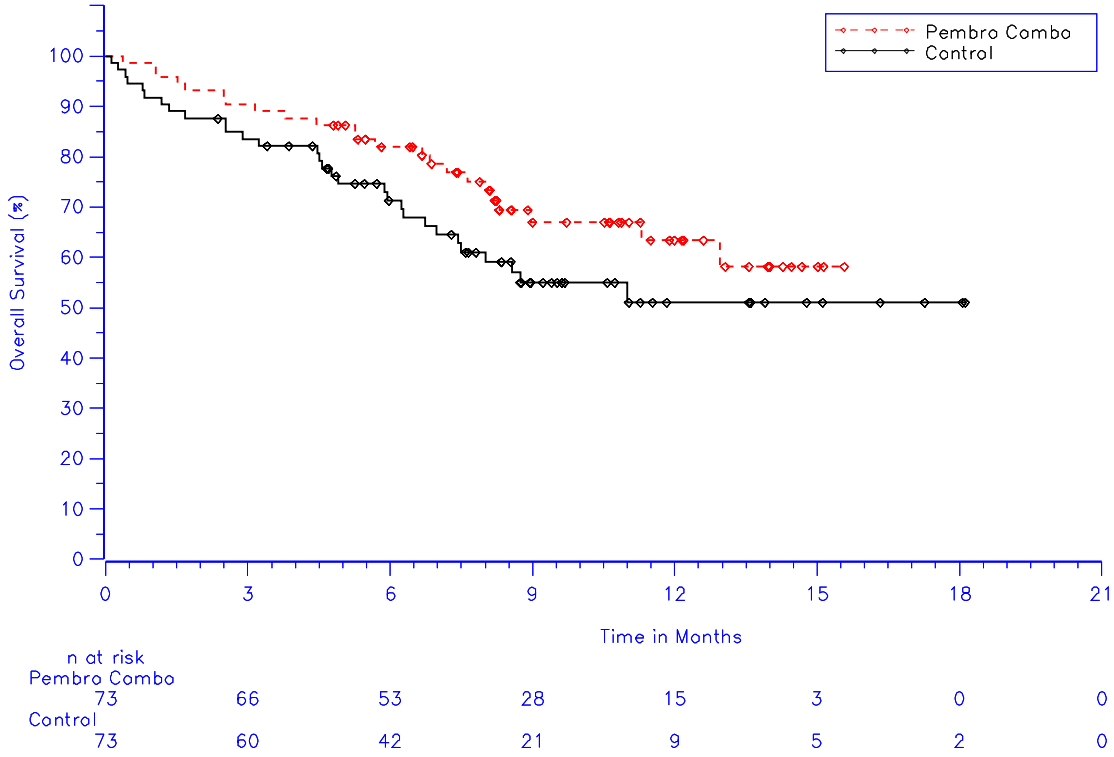
Source: Clinical study report[4]

Figure 7: KM estimates of OS (ITT population; TPS 1-49%)



Source: Clinical study report[4]

Figure 8: KM estimates of OS (ITT population; TPS ≥50%)



Source: Clinical study report[4]

B.2.6.3 Progression free survival[4, 35]

Progression free survival (PFS) is defined as time from randomisation to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first, expressed in days. Patients without an event (progression or death) at the time of last tumour assessment were considered right censored at the last disease assessment date.

A total of 349 (62%) PFS events had been reported at the time of data cut-off, 152 (54.7%) in the pembrolizumab combination group and 197 (70.1%) in the control arm.

Based on BICR assessment, median PFS for pembrolizumab combination was 6.4 months (95% CI 6.2, 8.3) compared with 4.8 months (95% CI 43, 5.7) for the control arm. This was a statistically significant and clinically meaningful benefit in PFS, equating to a 44% reduction in risk of progression or death for the pembrolizumab combination compared with the control (HR 0.56; 95% CI: 0.45, 0.70; p<0.0001) (Table 18). The PFS benefit for the pembrolizumab combination was maintained at 12 months; 31.3% of patients in the pembrolizumab combination and 14.4% of patients in the control were alive and progression-free (Table 19).

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 9).

Table 18: Analysis of PFS based on BICR per RECIST 1.1 (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control Hazard Ratio‡ (95% CI)‡ p-value‡‡
Pembrolizumab combination	278	152 (54.7)	1716.9	8.9	6.4 (6.2, 8.3)	[redacted]	0.56 (0.45, 0.70) P<0.0001
Control	281	197 (70.1)	1358.1	14.5	4.8 (4.3, 5.7)	[redacted]	

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cut-off Date: 03APR2018

Source: Clinical study report[4]; Paz-Ares 2018[35]

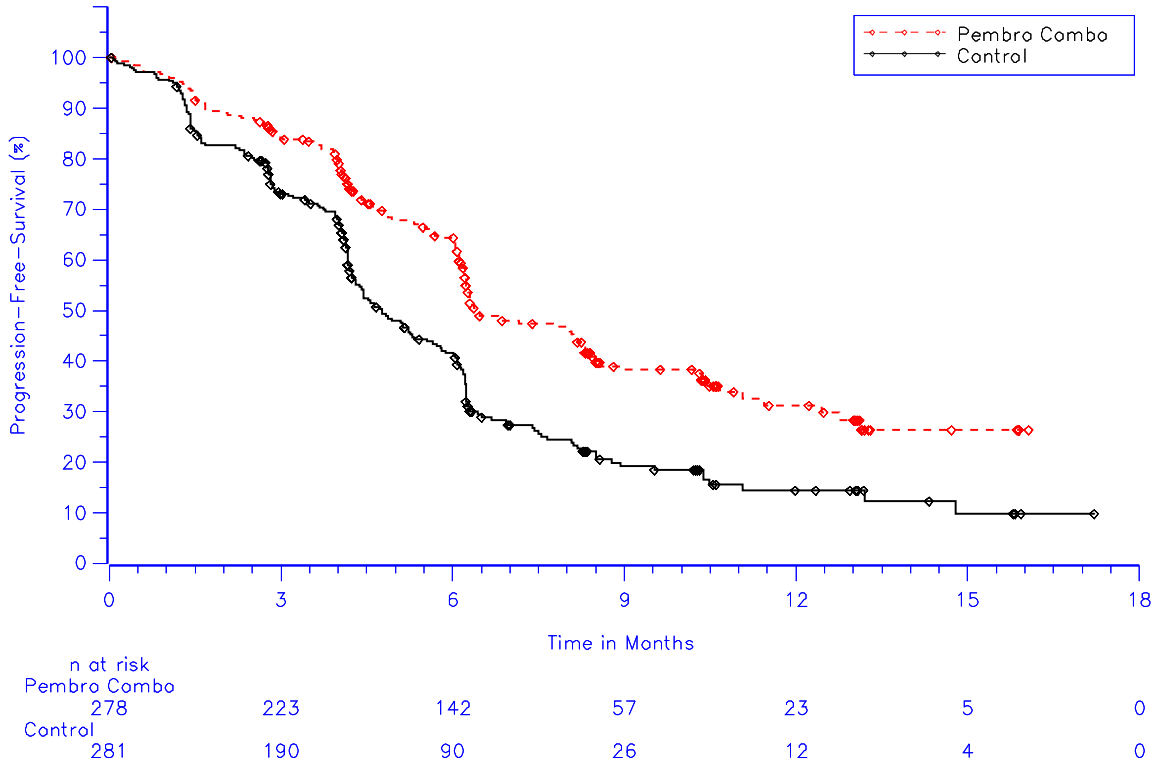
Table 19: Summary of PFS rate over time based on BICR per RECIST1.1 (ITT population)

	Pembrolizumab combination (N=278) % (95% CI)†	Control (N=281) % (95% CI)†
Summary of PFS rate at time point		
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	31.3 (24.1, 38.7)	14.4 (9.4, 20.5)

† From product-limit (Kaplan-Meier) method for censored data.
Database cut-off date: 03APR2018

Source: Clinical study report[4]

Figure 9: Kaplan-Meier estimates of PFS based on BICR per RECIST 1.1 (ITT population)



Source: Clinical study report[4]

Results of PFS evaluation based on investigator assessment (RECIST 1.1) were consistent with those from the primary analysis. (Table 20, Table 21, Figure 10)

Table 20: PFS based on investigator assessment per RECIST 1.1 (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control Hazard Ratio‡ (95% CI)‡ p-value‡‡
Pembrolizumab combination	278	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Control	281	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
‡‡ One-sided p-value based on stratified log-rank test.
Database Cut-off Date: 03APR2018

Source: Clinical study report[4]

Table 21: Summary of PFS based on investigator assessment per RECIST 1.1 over time (ITT population)

	Pembrolizumab combination (N=278) % (95% CI)†	Control (N=281) % (95% CI)†
Summary of PFS rate at time point		
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.
Database cut-off date: 03APR2018

Source: Clinical study report[4]

Figure 10: Kaplan-Meier estimates of PFS based on investigator assessment per RECIST 1.1 (ITT population)

Source: Clinical study report[4]

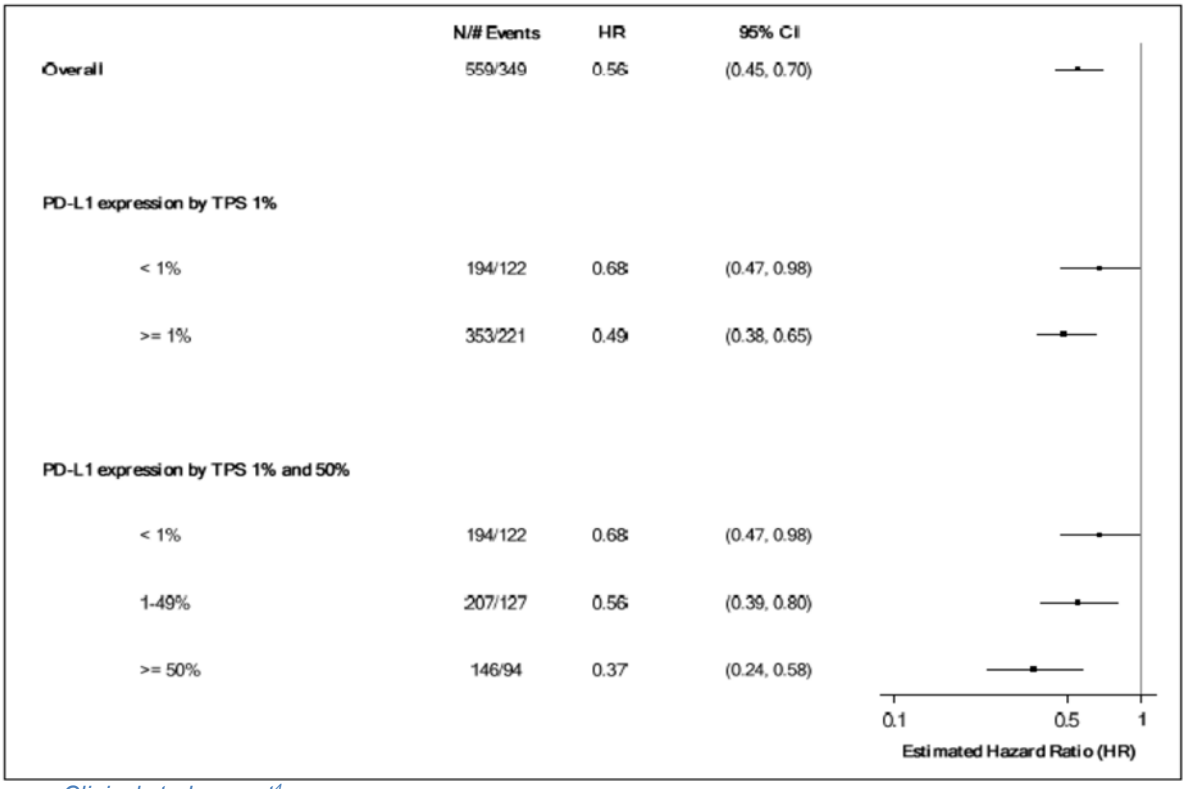
PFS by PD-L1 expression

A clinically meaningful improvement in PFS in the pembrolizumab combination compared with the control was observed across all PD-L1 expression status subgroups. An incremental improvement in PFS HR (0.68, 0.56, and 0.37) was observed with increasing PD-L1 expression status (TPS <1%, TPS 1-49%, and TPS ≥50%, respectively). (Figure 9)

Median PFS was longer in the pembrolizumab combination than control in each of the PD-L1 subgroups: TPS <1% (6.3 vs 5.3 months); TPS 1 to 49% (7.2 vs 5.2 months); TPS ≥50% (8.0 vs 4.2 months).(Table 22)

In all PD-L1 subgroups analysed, the PFS KM curves for the two treatment groups separated early and remained separated throughout the evaluation period, demonstrating a consistent effect of the pembrolizumab combination on PFS, regardless of PD-L1 expression status. (Figure 12, Figure 13, Figure 14)

Figure 11: Forest plot of PFS hazard ratio by PD-L1 expression based on BICR per RECIST 1.1 (ITT population)



Source: Clinical study report[4]

Table 22: Analysis of PFS by PD-L1 expression based on BICR per RECIST 1.1 (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control Hazard Ratio‡ (95% CI)‡ p-value‡‡
TPS<1%							
Pembrolizumab combination	95	55 (57.9)	557.1	9.9	6.3 (6.1, 6.5)	65.7 (54.6, 74.7)	0.68 (0.47, 0.98) p=0.0177
Control	99	67 (67.7)	508.9	13.2	5.3 (4.4, 6.2)	46.7 (35.8, 57.0)	
TPS 1-49%							
Pembrolizumab combination	103	54 (52.4)	656.7	8.2	7.2 (6.0, 11.4)	61.9 (51.1, 71.0)	0.56 (0.39, 0.80) p=0.0008
Control	104	73 (70.2)	526.5	13.9	5.2 (4.2, 6.2)	48.8 (38.3, 58.4)	
TPS≥50%							
Pembrolizumab combination	73	39 (53.4)	449.4	8.7	8.0 (6.1, 10.3)	67.0 (54.2, 77.0)	0.37 (0.24, 0.58) p<0.0001
Control	73	55 (75.3)	296.8	18.5	4.2 (2.8, 4.6)	23.0 (13.3, 34.2)	

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

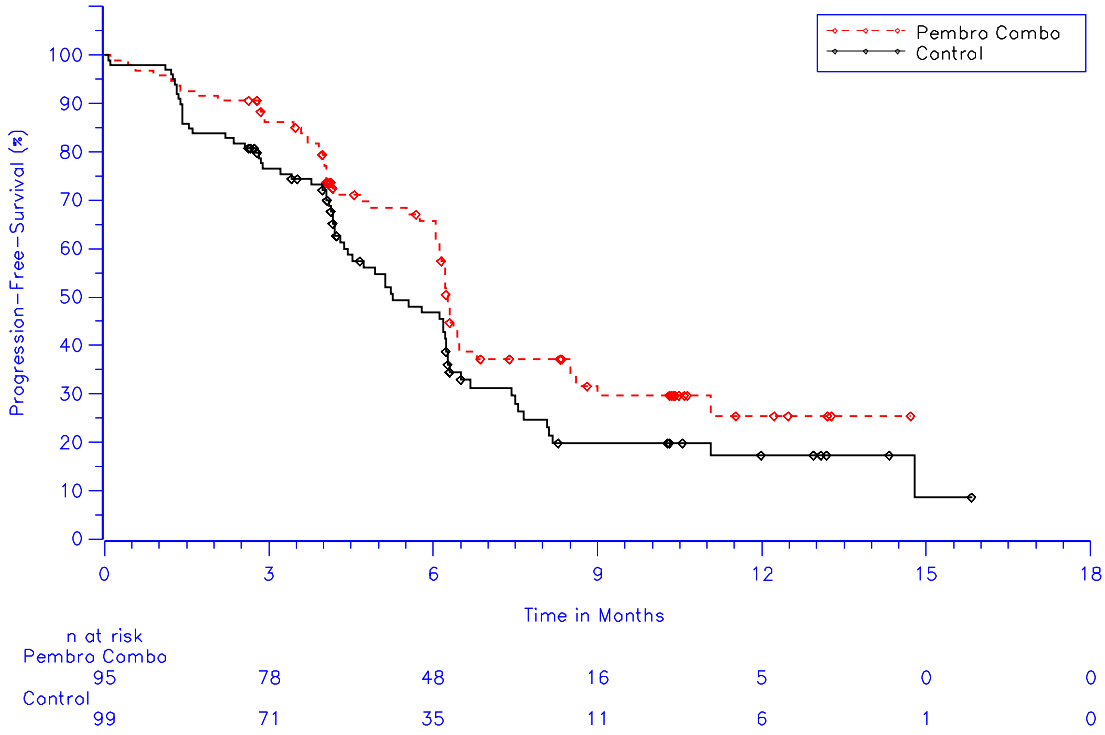
‡ Based on Cox regression model with treatment as covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).

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

Database Cut-off Date: 03APR2018

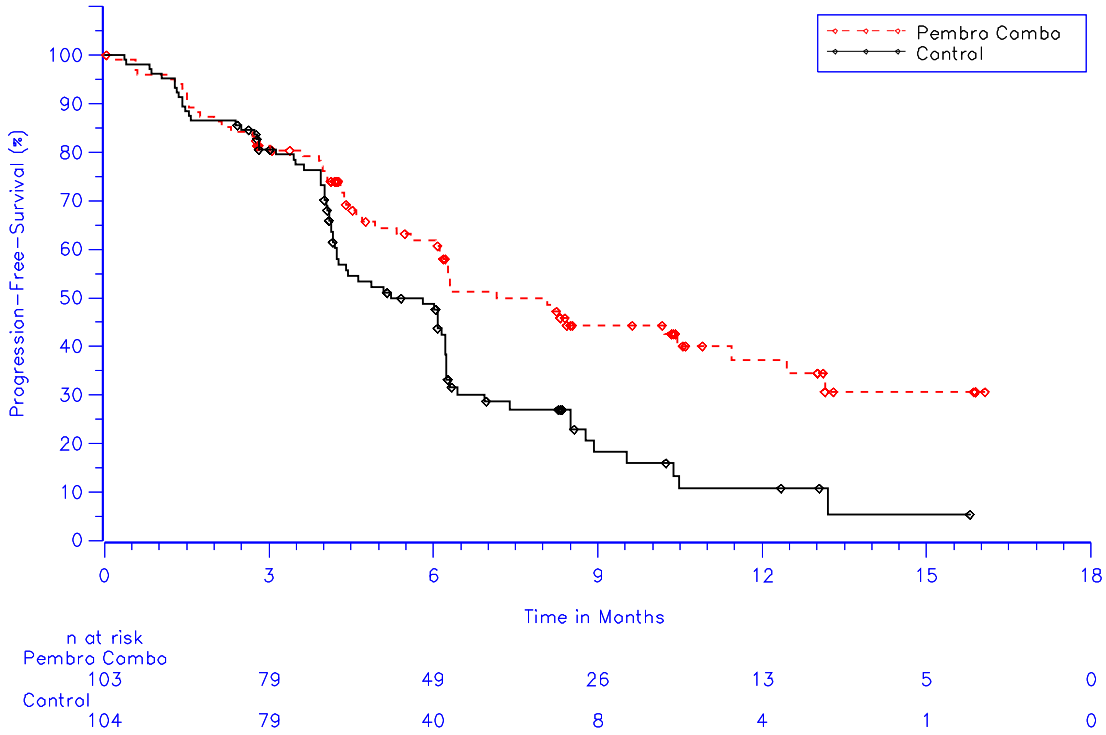
Source: Clinical study report[4]

Figure 12: Kaplan-Meier estimates of PFS based on BICR per RECIST 1.1 (ITT population; TPS<1%)



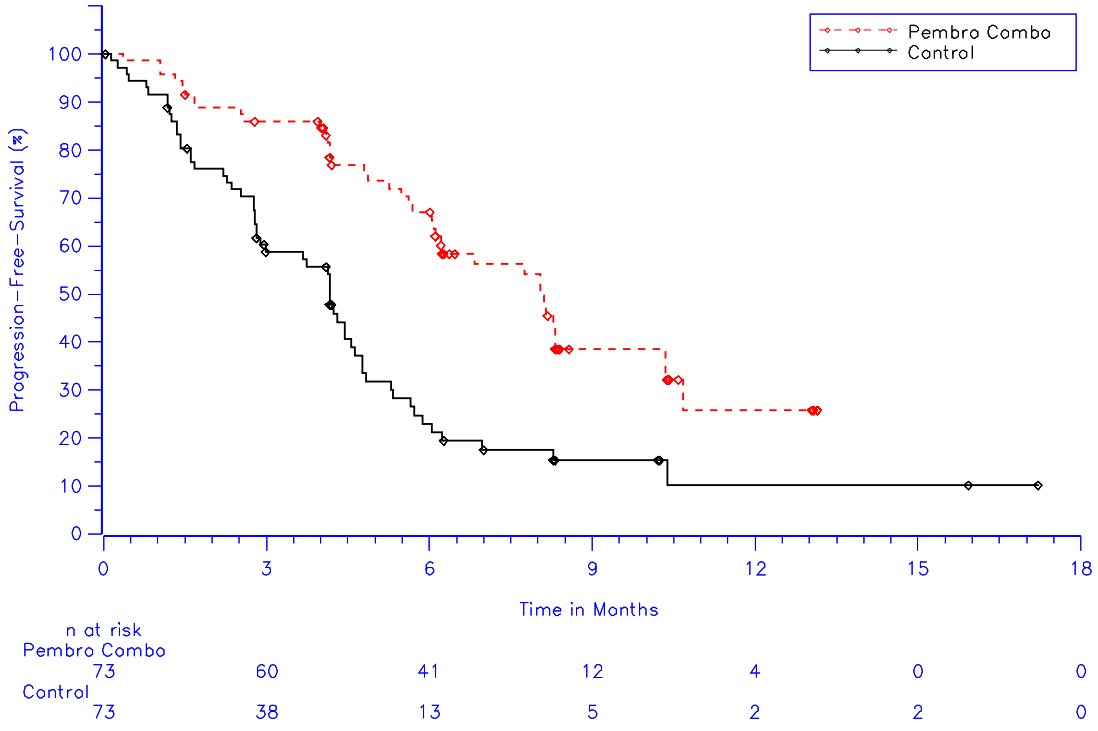
Source: Clinical study report[4]

Figure 13: Kaplan-Meier estimates of PFS based on BICR per RECIST 1.1 (ITT population; TPS 1-49%)



Source: Clinical study report[4]

Figure 14: Kaplan-Meier estimates of PFS based on BICR per RECIST 1.1 (ITT population; TPS ≥50%)



Source: Clinical study report[4]

B.2.6.4 Objective response rate[4, 35]

Overall Response Rate (ORR) is defined as the proportion of subjects who have a complete response (CR) or a partial response (PR). Responses were based on confirmed assessments by BICR review per RECIST 1.1. Best Overall Response (BOR) per RECIST 1.1 as assessed by BICR of imaging is summarized using number and percentages by treatment arm. ORR and BOR were also assessed by the investigator using RECIST 1.1.

The pembrolizumab combination provided a statistically significant improvement in confirmed ORR based on BICR per RECIST 1.1 when compared with the control (57.9% vs 38.4%). Statistical assessment of the difference between the treatment groups favoured the pembrolizumab combination (19.5% difference; p<0.0001) relative to the control (Table 23).

The difference in the ORR between treatment groups was primarily driven by the PR rates, with the pembrolizumab combination demonstrating a higher rate of PR (56.5%) than the control (36.3%). The observed rate of progressive disease as the best overall response was considerably lower in the pembrolizumab combination (6.1%) than in the control (13.9%), offering further support for the benefit of adding pembrolizumab to chemotherapy. (Table 24)

Table 23: Analysis of confirmed OR based on BICR per RECIST 1.1 (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value††
Pembrolizumab combination	278	161	57.9 (51.9,63.8)	19.5 (11.2,27.5)	<0.0001
Control	281	108	38.4 (32.7,44.4)		

† Based on Miettinen & Nurminen method stratified by PD-L1 status (TPS ≥ 1% vs. <1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Database Cut-off Date: 03APR2018

Source: Clinical study report[4]

Table 24: Summary of confirmed OR based on BICR per RECIST 1.1 (ITT population)

	Pembrolizumab combination			Control		
	n	(%)	(95% CI)	N	(%)	(95% CI)
Number of Patients in Population	278			281		
Complete Response (CR)	4	1.4	[redacted]	6	2.1	[redacted]
Partial Response (PR)	157	56.5	[redacted]	102	36.3	[redacted]
Objective Response (CR+PR)	161	57.9	(51.9, 63.8)	108	38.4	(32.7. 44.4)
Stable Disease (SD)	78	28.1	[redacted]	104	37.0	[redacted]
Disease Control (CR+PR+SD)	239	86.0	[redacted]	212	75.4	[redacted]
Progressive Disease (PD)	17	6.1	[redacted]	39	13.9	[redacted]
Not Evaluable (NE)	6	2.2	[redacted]	7	2.5	[redacted]
Not Assessable	16	5.8	[redacted]	23	8.2	[redacted]

Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Stable disease includes both SD and Non-CR/Non-PD.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s)
being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cut-off Date: 03APR2018.

Source: Clinical study report[4]

Confirmed ORR based on investigator assessment per RECIST 1.1 was consistent with the assessment by BICR. (Table 25; Table 26)

Table 25: Analysis of confirmed OR based on investigator assessment per RECIST 1.1 (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab combination	278	153	55.0 (49.0,61.0)	23.5 (15.4,31.3)	<0.0001
Control	281	89	31.7 (26.3,37.5)		

[†] Based on Miettinen & Nurminen method stratified by PD-L1 status (TPS ≥ 1% vs. <1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on investigator assessment per RECIST 1.1.
Database Cut-off Date: 03APR2018

Source: Clinical study report[4]

Table 26: Summary of confirmed OR based on investigator assessment per RECIST 1.1 (ITT population)

	Pembrolizumab combination			Control		
	n	(%)	(95% CI)	N	(%)	(95% CI)
Number of Patients in Population	278			281		
Complete Response (CR)	2	0.7	[redacted]	0	0	[redacted]
Partial Response (PR)	151	54.3	[redacted]	89	31.7	[redacted]
Objective Response (CR+PR)	153	55.0	(49.0, 61.0)	89	31.7	(26.3, 37.5)
Stable Disease (SD)	80	28.8	[redacted]	124	44.1	[redacted]
Disease Control (CR+PR+SD)	233	83.8	[redacted]	213	75.8	[redacted]
Progressive Disease (PD)	25	9.0	[redacted]	39	13.9	[redacted]
Not Evaluable (NE)	4	1.4	[redacted]	6	2.1	[redacted]
Not Assessable	16	5.8	[redacted]	23	8.2	[redacted]

Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Stable disease includes both SD and Non-CR/Non-PD.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s)
being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.
Database Cut-off Date: 03APR2018.

Source: Clinical study report[4]

ORR by PD-L1 expression

A clinically meaningful improvement in ORR in the pembrolizumab combination compared with control was observed across each of the PD-L1 expression subgroups assessed (TPS<1%, TPS 1-49% and TPS ≥50%. (Figure 15; Table 27).

Figure 15: Forest plot of confirmed ORR by PD-L1 expression based on BICR per RECIST 1.1 (ITT population)

Source: Clinical study report[4]

Table 27: Analysis of confirmed ORR by PD-L1 expression based on BICR per RECIST 1.1 (ITT population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value††
TPS<1%					
Pembrolizumab combination	95	60	63.2 (52.6,72.8)	23.0 (8.8,36.2)	0.0008
Control	99	40	40.4 (30.7,50.7)		
TPS 1-49%					
Pembrolizumab combination	103	51	49.5 (39.5,59.5)	8.0 (-5.5,21.3)	0.1235
Control	104	43	41.3 (31.8,51.4)		
TPS≥50%					
Pembrolizumab combination	73	44	60.3 (48.1,71.5)	27.5 (11.3,42.3)	0.0005
Control	73	24	32.9 (22.3,44.9)		

† Based on Miettinen & Nurminen method stratified by PD-L1 status (TPS ≥ 1% vs. <1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded independent central review.
Database Cut-off Date: 03APR2018

Source: Clinical study report[4]

B.2.6.5 Duration of response and Time to response[4, 35]

Duration of Response (DOR) is defined as the time from the first documented evidence of CR/PR until disease progression (PD) or death. Time to Response (TTR) is defined as the time from randomization to the first assessment of a complete response or partial response (CR/PR). Only confirmed CR/PRs are included in the analysis for TTR and DOR. Subjects without PD or death are censored at the time of last tumour assessment. Responses are based on confirmed assessments by BICR review per RECIST 1.1. TTR and DOR are also assessed by the investigator using RECIST 1.1.

The pembrolizumab combination yielded a longer median DOR compared with the control (7.7 months vs 4.8 months) and more participants had extended responses for ≥6 months ([redacted] % vs [redacted] %) and ≥9 months ([redacted] % vs [redacted] %) by KM estimation.(Table 28) There was clear separation of the KM curves after Month 3 favouring the pembrolizumab

combination. (Figure 16) The median time to response was 1.4 months in both treatment groups.

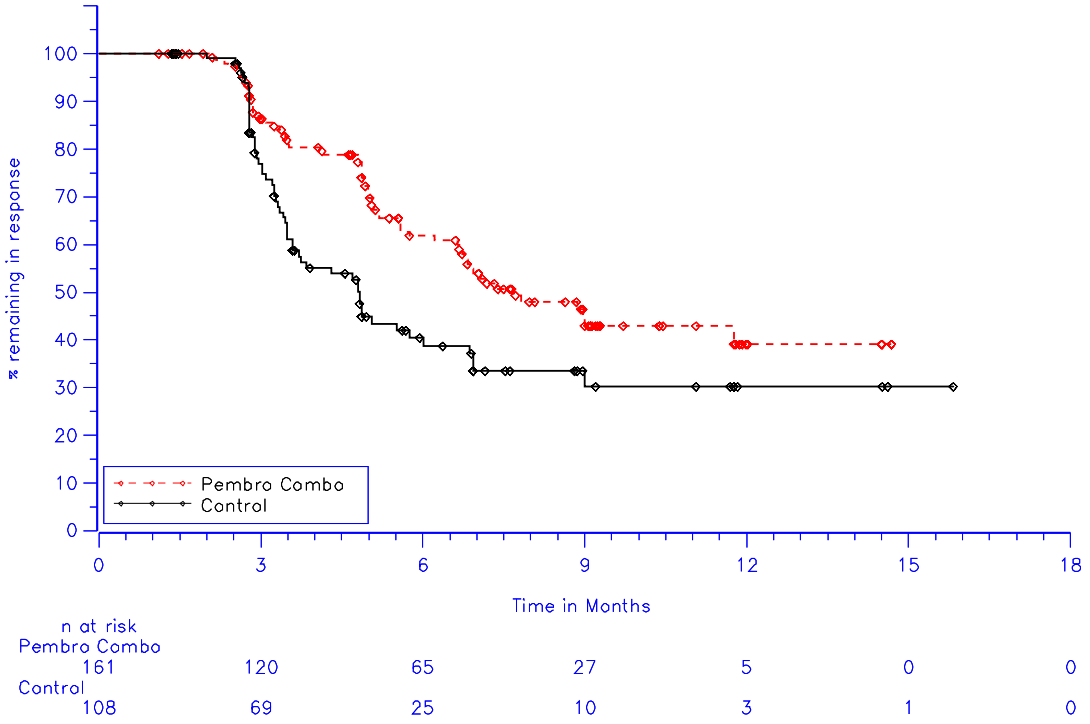
Table 28: Summary of TTR and DOR for subjects with confirmed response based on BICR per RECIST 1.1 (ITT population)

	Pembrolizumab combination (N=278)	Control (N=281)
Number of Subjects with Response† (%)	161	108
Time to Response† (months)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	1.4 (1.1-6.1)	1.4 (1.0-4.5)
Response Duration‡ (months)		
Median (Range)§	7.7 (1.1+ - 14.7+)	4.8 (1.3+ - 15.8+)
Number (% ‡) of Subjects with Extended Response Duration:		
≥ 3 months	[redacted]	[redacted]
≥ 6 months	[redacted]	[redacted]
≥ 9 months	[redacted]	[redacted]
≥ 12 months	[redacted]	[redacted]

† Response: best objective response as confirmed complete response or partial response.
‡ From product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
BICR = Blinded independent central review.
Database Cut-off Date: 03APR2018

Source: Clinical study report[4]

Figure 16: Kaplan-Meier estimates of DOR for subjects with confirmed response based on BICR per RECIST 1.1 (ITT population)



Source: Clinical study report[4]

Among confirmed responders, fewer participants progressed or died in the pembrolizumab combination (41.6%) compared with the control (52.8%). As of the data cut-off date, the proportion of participants with ongoing responses ≥6 months was higher for the pembrolizumab combination (29.8%) compared with the control (18.5%). (Table 29)

Table 29: Summary of response outcome in subjects with confirmed response based on BICR per RECIST 1.1 (ITT population)

	Pembrolizumab combination (N=278)	Control (N=281)
Number of Subjects with Response†	161	108
Subjects who progressed or died‡ (%)	[redacted]	[redacted]
Range of DOR (months)	[redacted]	[redacted]
Censored subjects (%)	[redacted]	[redacted]
who missed 2 or more consecutive disease assessments	[redacted]	[redacted]
who started new anti-cancer treatment	[redacted]	[redacted]
who were lost to follow-up	[redacted]	[redacted]
whose last adequate assessment was ≥5 months prior to data cut-off date	[redacted]	[redacted]
Ongoing response§	[redacted]	[redacted]
≥ 3 months	[redacted]	[redacted]
≥ 6 months	[redacted]	[redacted]
≥ 9 months	[redacted]	[redacted]
≥ 12 months	[redacted]	[redacted]
Range of DOR (months)	1.1+ to 14.7+	1.4 + to 15.8 +

† Includes subjects with a confirmed complete response or partial response.
‡ Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.
§ Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to followup,
and whose last disease assessment was <5 Months prior to data cut-off date.
For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in
the censoring criterion that occurred earliest.
'+' indicates there was no progressive disease by the time of last disease assessment.
BICR = Blinded independent central review.
Database Cut-off Date: 03APR2018

Source: Clinical study report[4]

The results from investigator assessment of DOR were consistent with those from the BICR assessment. (Table 30)

Table 30: Summary of TTR and DOR for subjects with confirmed response based on investigator assessment per RECIST 1.1 (ITT population)

	Pembrolizumab combination (N=278)	Control (N=281)
Number of Subjects with Response†	153	89
Time to Response† (months)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	1.4 (1.1-6.2)	1.4 (1.0-8.3)
Response Duration‡ (months)		
Median (Range)§	7.3 (1.1+ - 14.5+)	4.9 (1.2+ - 14.6+)
Number (% ‡) of Subjects with Extended Response Duration:		
≥ 3 months	[redacted]	[redacted]
≥ 6 months	[redacted]	[redacted]
≥ 9 months	[redacted]	[redacted]
≥ 12 months	[redacted]	[redacted]

† Response: best objective response as confirmed complete response or partial response.
‡ From product-limit (Kaplan-Meier) method for censored data.
§ "+" indicates there is no progressive disease by the time of last disease assessment.
NR = Not Reached.
Database Cut-off Date: 03APR2018

Source: Clinical study report[4]

Figure 17: Kaplan-Meier estimates of DOR for subjects with confirmed response based on investigator assessment per RECIST 1.1 (ITT population)

Source: Clinical study report[4]

B.2.6.6 Patient reported outcomes[4]

Three patient reported outcomes (PRO) questionnaires were employed to assess patient HRQoL in the study: EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D VAS. The PROs were analysed in the PRO Full analysis set (FAS) population (n=554), which consisted of all randomised patients who received at least 1 dose of study medication and completed at least 1 PRO assessment.

Of particular relevance to this submission is the EQ-5D VAS PRO, which was used to characterise the utility values included in the cost-effectiveness model (see Section B.3). Compliance rates for EQ-5D VAS were [redacted] % and [redacted] % at baseline for the pembrolizumab combination and control groups, respectively. Completion rates decreased at time points post baseline as more patients discontinued the study.

Results from the EQ-5D VAS analyses indicate that the addition of pembrolizumab to carboplatin/paclitaxel (or nab-paclitaxel) improved disease related symptoms and did not exacerbate treatment-related symptoms in the study population. At week 9, when patients were still receiving chemotherapy, stability from baseline on EQ-5D-3L VAS score was

observed in the pembrolizumab combination group compared to a slight decline in the control arm (-1.26); however, there was no statistically significant difference between the treatment groups. At week 18, when patients were no longer receiving chemotherapy, the pembrolizumab combination group showed a slight increase over baseline in EQ-5D-3L VAS scores (LS Mean [redacted]; 95% CI [redacted]), while the control group showed a slight decrease (LS Mean [redacted]; 95% CI [redacted]). The difference between the treatment groups on EQ-5D-3L VAS score at Week 18 was statistically significant (LS Means [redacted]; 95% CI [redacted] p= [redacted]). (Table 31)

Section B.3.4 provides further details of the EQ-5D and utilities data used in the cost-effectiveness model. Further details of the EORTC QLQ-C30, EORTC QLQ-LC13 are presented in Section 11.5 of the KEYNOTE-407 company CSR. [4]

Table 31: Analysis of EQ-5D VAS change from baseline to week 9 and to week 18 (FAS population)

	Baseline		week 9		Change from Baseline at week 9	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Week 9						
Pembrolizumab combination	255	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Control	266	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
Pembrolizumab combination vs. Control					[redacted]	[redacted]
Week 18						
Pembrolizumab combination	255	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Control	266	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					Difference in LS Means (95% CI)	p-Value
Pembrolizumab combination vs. Control					[redacted]	[redacted]

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (PD-L1 expression (tumor proportion score ≥ 1% vs. <1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia)) as covariates.

For baseline and week 9, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

P-value is based on two-sided t test.

Database Cut-off Date: 03APR2018

Source: Clinical study report[4]

B.2.7 Subgroup analysis [40]

A series of subgroup analyses was pre-specified in the KEYNOTE-407 study protocol to assess the between-group treatment effect on OS, PFS and ORR of the following variables:

- Age category (<65, ≥65 years)
- ECOG Performance Scale (0, 1)
- Sex (female, male)
- Race (white, non-white)
- Geographic region (East Asia, Non-East Asia)
- Geographic region (EU, non-EU)
- PD-L1 expression (unknown, TPS <1%, or TPS ≥1%)
- Taxane chemotherapy (paclitaxel, nab-paclitaxel)

Results of the subgroup analyses based on PD-L1 expression levels have been presented in Section B.2.6 above. In this section, we provide a summary of the results of the other subgroup analyses.

Based on the analyses conducted, the OS, PFS and ORR benefit of pembrolizumab combination over the control was observed in all subgroups, as depicted in the Forest plots below. Full results of the subgroup analyses are presented in Appendix E.

Figure 18: Forest plot of OS hazard ratio by subgroup factors (ITT population)

For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. Non-East Asia). For other subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
Subjects with PD-L1 not evaluable are not included in the subgroup analysis.
If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot.
Database Cut-off Date: 03APR2018
Source: Clinical study report[4]

Figure 19: Forest plot of PFS hazard ratio by subgroup factors based on BICR assessment per RECIST 1.1 (ITT population)

For overall population and the PD-L1 subgroup, analysis is based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. Non-East Asia). For other subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
Subjects with PD-L1 not evaluable are not included in the analysis for PD-L1 subgroup.
If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot.
Database Cut-off Date: 03APR2018
Source: Clinical study report[4]

Figure 20: Forest plot of confirmed ORR by subgroup factors based on BICR per RECIST 1.1 (ITT population)

Analysis (ORR difference and 95% CI) for the overall population and the PD-L1 subgroup is based on the stratified Miettinen & Nurminen method; analysis for the other subgroups is based on the unstratified Miettinen & Nurminen method.
If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup is not displayed in the plot.
Subjects with PD-L1 not evaluable are not included in the analysis for PD-L1 subgroup variable.
Database Cut-off Date: 03APR2018
Source: Clinical study report[4]

.2.8 Meta-analysis

With only one RCT having been conducted to provide evidence of safety and efficacy for pembrolizumab combination therapy versus a relevant comparator in the squamous NSCLC population (KEYNOTE-407), meta-analysis was neither necessary nor feasible.

B.2.9 Indirect treatment comparisons

In order to supplement the direct evidence for pembrolizumab combination from KEYNOTE-407, and in the absence of head to head RCTs of pembrolizumab combination versus all relevant comparators, two separate indirect treatment comparisons were conducted as follows:

- ITC1: Pembrolizumab combination versus chemotherapy comparators [41]
- ITC2: Pembrolizumab combination versus pembrolizumab monotherapy.[42]

In this section, we present the results of the ITCs which inform our cost-effectiveness model. Additional analyses were also conducted, full details of which are provided in Appendix D1.2 along with the methodologies adopted to construct both ITCs.

B.2.9.1 Pembrolizumab combination versus chemotherapy[41]

In the absence of head to head RCTs of pembrolizumab combination versus relevant chemotherapy comparators (as per the Decision Problem), an ITC was conducted. The ITC, by means of network meta-analysis (NMA) of RCTs, assessed the relative treatment effects for the outcomes required to inform the cost-effectiveness model: overall survival (OS) and progression-free survival (PFS) for pembrolizumab combination versus competing interventions used routinely in UK clinical practice. The NMA also provided evidence of the comparative efficacy of the platinum-based chemotherapy regimens routinely used in the UK.

Evidence base

The 36 relevant RCTs identified in the SLR were included in the NMA feasibility assessment; of these, five were conducted in purely squamous patients (CTONG 1002, KEYNOTE-407, Kristensen et al., 2017, NAVotrial03, and Saad et al., 2017) and the remaining 31 were conducted in patients unselected for histology. Given the evidence base available, two separate NMAs were conducted to provide comparative efficacy data:

- NMA 1: Squamous, PD-L1 unselected (based on the 5 studies in purely squamous patients)
- NMA 2: Unselected for histology, PD-L1 unselected (based on the remaining 31 studies)

Study characteristics for all 36 included RCTs are summarised in Appendix D1.2.2.

Feasibility assessment overview

During the feasibility assessment, the comparability of the included trials was assessed in terms of histology and other potential prognostic factors. Of the 36 trials identified in the SLR, 11 trials were excluded from the NMA. Three trials (Ahmed et al., 2017, ECOG 1599, and Khodadad et al., 2014) were removed from the unselected for histologies analysis because most enrolled patients had an ECOG performance status of 2, whereas other trials included mostly patients with ECOG scores of 0 or 1. Three trials (Chen et al., 2006, Kristensen et al., 2017, and NVALT-3) were removed as they were conducted exclusively in elderly patients. The publications associated with NAVotrial03, GOIM 2608, and Sumanth et al., 2008 did not provide HRs or KMs for OS or PFS. Finally, both KEYNOTE-024 and KEYNOTE-042 were removed from the analysis as pembrolizumab monotherapy is only indicated in high PD-L1 expressors (PD-L1 ≥ 50%) in the UK and the target population for analyses conducted were patients not selected by PD-L1 expression level.

Overview of analyses

Networks were constructed to compare pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin (any PD-L1 status) to competing interventions in squamous patients. The squamous (PD-L1 unselected) network contained only trials conducted in exclusively squamous patients. Additionally, networks pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin (any PD-L1 status) were constructed to assess treatment efficacy compared to competing interventions in unselected for histology patients. The unselected for histology (PD-L1 unselected) networks included trials that did not select patients based on histology status in addition to squamous-only trials. Therefore, meta-regression was employed in unselected for histology NMAs to estimate treatment effects in a squamous population as this was the population of interest.

In the networks including unselected for histology studies, a covariate representing the proportion of non-squamous patients in each trial was incorporated into the model to account for the impact of different histological distributions within trials on treatment effects. In cases

where the proportion of squamous patients was not reported for the trial, the imputed mean of all trials reporting proportion squamous was used. In analyses using a non-squamous covariate, the covariate was centred at zero, in order to calculate treatment effects relative to a pure squamous population, the population of interest. If trials reported, squamous subgroup data, this was utilized rather than all-comer, unselected for histology data. Squamous subgroup data was only available for ECOG 1594.

Following the removal of trials that were outliers for various potential relative treatment effect modifiers and the incorporation of a covariate to adjust for histology in the unselected for histology networks, the remaining trials in the analysis networks were deemed to be reasonably similar and differences in trial or patient characteristics were not considered likely to bias indirect comparison. Data sources for clinical endpoints included in the analyses by histology subgroup or unselected histologies are presented in Table 32

Table 32: Data sources for NMA by trial

Trial	Publications	HR (OS)	HR (PFS)	TTP/TTF/PFS indicator	KM (OS)	KM (PFS)	TTP/TTF/PFS Indicator
Chang 2008*	Chang et al., 2008[43]	**Figure 1**	–	–	Figure 1	–	–
Chen 2004*	Chen et al., 2004[44]	**Figure 2**	**Figure 1**	TTP	Figure 2	Figure 1	TTP
Chen 2007*	Chen et al., 2007[45]	**Figure 2**	**Figure 1**	TTP	Figure 2	Figure 1	TTP
Comella 2000	Comella et al., 2000a[46]	Page 1451	–	–	Figure 1	–	–
	Comella et al., 2000b[47]	–	–	–	–	–	–
	Comella et al., 2000c[48]	–	–	–	–	–	–
CTONG 1002	Yang et al.,) 2014[49]	Page 1 (text)	–	PFS	–	–	–
	Yang et al., 2014[50]	–	–	–	–	–	–
Douillard 2005	Douillard et al., 2005[51]	**Figure 2**	–	–	Figure 2	–	–
ECOG 1594	Hoang et al., 2013[52]	**Page 8**	**Page 9**	PFS	Page 8	Page 9	PFS
	Schiller et al., 2002[39]	–	–	–	–	–	–
	Sweeney et al., 2001[53]	–	–	–	–	–	–
EORTC 08975	Smit et al., 2003[54]	**Figure 2**	**Figure 3**	PFS	Figure 2	Figure 3	PFS
FACS*	Ohe et al., 2007[55]	**Figure 1**	Figure 1	TTP	**Figure 1**	Figure 1	TTP
	Takeda et al., 2003[56]	–	–	–	–	–	–
	Kubota et al., 2014[57]	–	–	–	–	–	–

Trial	Publications	HR (OS)	HR (PFS)	TTP/TTF/PFS indicator	KM (OS)	KM (PFS)	TTP/TTF/PFS Indicator
	Goto et al., 2006[58]	–	–	–	–	–	–
Ferry 2017	Ferry et al., 2017[59]	Figure 2B	–	–	Figure 2A	–	–
Gebbia 2003	Gebbia et al., 2003[60]	**Figure 3**	**Figure 2**	TTP	Figure 3	Figure 2	TTP
GFPC 99-01	Thomas et al., 2006[61]	**Figure 2**	**Figure 1**	TTP	Figure 2	Figure 1	TTP
GLOB 3	Tan et al., 2009[62]	–	Figure 2	TTF	–	Figure 2	TTF
Helbekkmo 2007	Helbekkmo et al., 2007[63]	**Figure 2a**	–	–	Figure 2a	–	–
Kawahara 2013*	Kawahara et al., 2013[64]	Page 4633 (text)	Page 4633 (text)	PFS	Figure 3	Figure 2	PFS
KEYNOTE-407	Provided by Merck (data cutoff: April 3, 2018)	Confidential email	Confidential email	PFS	Confidential email	Confidential email	PFS
Martoni 2005	Martoni et al., 2005[65]	**Figure 4**	**Figure 3**	TTP	Figure 4	Figure 3	TTP
Rosell 2002	Rosell et al., 2002[66]	**Figure 3**	**Figure 2**	TTP	Figure 3	Figure 2	TTP
Mazzanti 2003	Mazzanti et al., 2003[67]	**Figure 1**	**Figure 2**	TTP	Figure 1	Figure 2	TTP
Saad 2017	Saad et al., 2017[68]	**Figure 3**	**Figure 2**	PFS	Figure 3	Figure 2	PFS
Scagliotti 2002	Scagliotti 2002[69]	Page 4287 (text)	Page 4287 (text)	TTP	Figure 1	Figure 2A	TTP
	Scagliotti 2009[70]	–	–	–	–	–	–
SWOG 9509	Kelly 2001[71]	**Figure 1**	--	--	Figure 1	--	--
	Moinpour et al, 2002[72]	–	–	–	–	–	–
TAX 326	Fossella 2003[73]	Table 2	--	–	Figure 1	--	–
	Belani 2001[74]	–	–	–	–	–	–
	Belani 2006[75]	–	–	–	–	–	–
TREAT 2010	Treat et al., 2010[76]	**Figure 3A**	**Figure 3B**	TTP	Figure 3A	Figure 3B	TTP
Zatloukal 2003	Zatloukal et al., 2003[77]	**Page 326**	**Page 326**	TTP	Page 326	Page 326	TTP

* denotes trials with 100% East Asian patients
Bold denotes HRs calculated from KM curves
Grey denotes trials that were not included in NMAs

Results of analyses

NMA 1: Squamous, PD-L1 unselected

Overall survival

Three trials evaluating 6 treatments composed the squamous, PD-L1 unselected network (Figure 21) for overall survival. The squamous (PD-L1 unselected) network contained only trials conducted in exclusively squamous patients. The results of the NMA are shown in (Table 33). The fixed effects model was chosen as a result of limited data availability; between-study heterogeneity could not be estimated as each node is connected by only one study. Time-varying results can be found in Appendix D.

Based on the fixed effects NMA of the squamous, PD-L1 unselected population, the point estimate of the HR for pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin versus all other interventions was less than one. Pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin was statistically superior to carboplatin + paclitaxel/nab-paclitaxel [HR: 0.64, 95% CrI: 0.48, 0.84], cisplatin + docetaxel [HR: 0.54, 95% CrI: 0.34, 0.87], and cisplatin + paclitaxel [HR: 0.46, 95% CrI: 0.29, 0.72]. Additionally, cisplatin + gemcitabine was statistically superior to cisplatin + paclitaxel [HR: 0.46, 95% CrI: 0.47, 1.00]. Platinum-based doublet regimens were not statistically different from one another, with one exception. Cisplatin + paclitaxel had statistically superior OS compared to cisplatin + gemcitabine [HR: 0.68, 95% CrI: 0.47, 1.00] in the pure squamous population.

Analysis of the results of the time-varying NMA fixed effects model show that the HR for all interventions versus carboplatin + paclitaxel/nab-paclitaxel (anchor treatment) did not vary over time; therefore, the proportional hazards assumption is considered plausible for this analysis. (See Appendix D1.2.3.1 for details for results of the time-varying NMAs)

Figure 21: Network of evidence for OS; squamous, PD-L1 unselected; hazard ratios

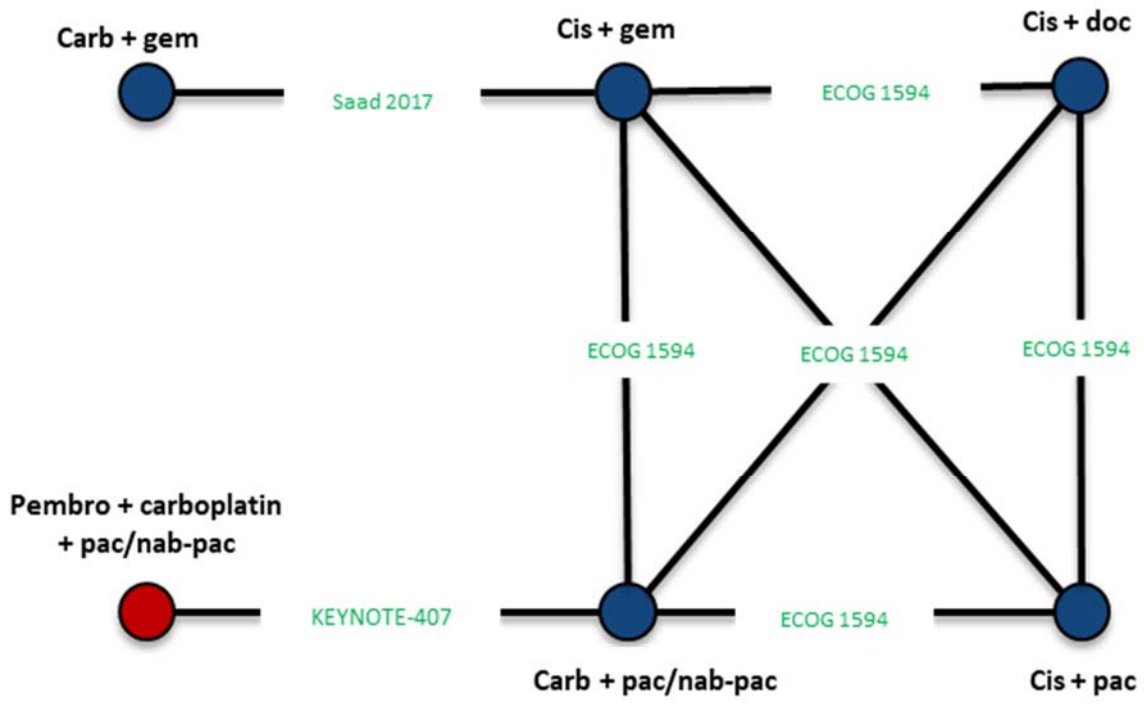


Table 33: Results of fixed effects network meta-analysis based on constant hazard ratio assumption; overall survival; squamous, PD-L1 unselected; results presented as constant hazard ratios between all competing interventions along with 95% credible intervals

Carb + gem	0.97 (0.47, 2.00)	0.82 (0.40, 1.70)	1.03 (0.55, 1.90)	0.70 (0.34, 1.44)	1.53 (0.71, 3.30)
1.03 (0.50, 2.11)	**Carb + pac or nab-pac**	0.85 (0.58, 1.24)	1.05 (0.72, 1.54)	0.72 (0.50, 1.05)	**1.56 (1.19, 2.07)**
1.22 (0.59, 2.48)	1.18 (0.81, 1.72)	**Cis + doc**	1.24 (0.85, 1.81)	0.85 (0.59, 1.23)	**1.84 (1.15, 2.93)**
0.97 (0.53, 1.81)	0.95 (0.65, 1.39)	0.81 (0.55, 1.17)	**Cis + gem**	**0.68 (0.47, 1.00)**	1.49 (0.94, 2.38)
1.42 (0.69, 2.92)	1.39 (0.95, 2.01)	1.18 (0.81, 1.70)	**1.46 (1.00, 2.12)**	**Cis + pac**	**2.17 (1.38, 3.44)**
0.66 (0.30, 1.42)	**0.64 (0.48, 0.84)**	**0.54 (0.34, 0.87)**	0.67 (0.42, 1.07)	**0.46 (0.29, 0.72)**	**Pembro + carb + pac or nab-pac**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 9.09; Deviance: 4.12

Progression-free survival

Progression-free survival was reported in three trials regarding 6 treatments in the squamous, PD-L1 unselected network (Figure 22). The squamous (PD-L1 unselected)

network contained only trials conducted in exclusively squamous patients. The results of the NMA are shown in Table 34. The fixed effects model was chosen due to paucity of trial data as well as only one trial connecting each treatment, thus between-study heterogeneity was not estimable. Time-varying results can be found in Appendix D1.2.3.1.

Based on the fixed effects NMA of the squamous, PD-L1 unselected population, the point estimate of the HR for pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin versus all other interventions was less than one. Pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin was statistically superior to all competing interventions in the network with HR point estimates ranging from 0.43 to 0.65. Additionally, cisplatin + gemcitabine was statistically superior to cisplatin + paclitaxel [HR: 0.66, 95% CrI: 0.46, 0.95]. Platinum-based doublet regimens were not statistically different from one another, with one exception. Cisplatin + paclitaxel had statistically superior PFS compared to cisplatin + gemcitabine [HR: 0.66, 95% CrI: 0.46, 0.95] in the pure squamous population.

Analysis of the time-varying NMA fixed effects model indicate that the HR for all interventions versus carboplatin + paclitaxel/nab-paclitaxel (anchor treatment) did not vary over time. Therefore, NMA results assuming proportional hazards over time are considered plausible for this analysis.

Figure 22: Network of evidence for PFS; squamous, PD-L1 unselected; hazard ratios

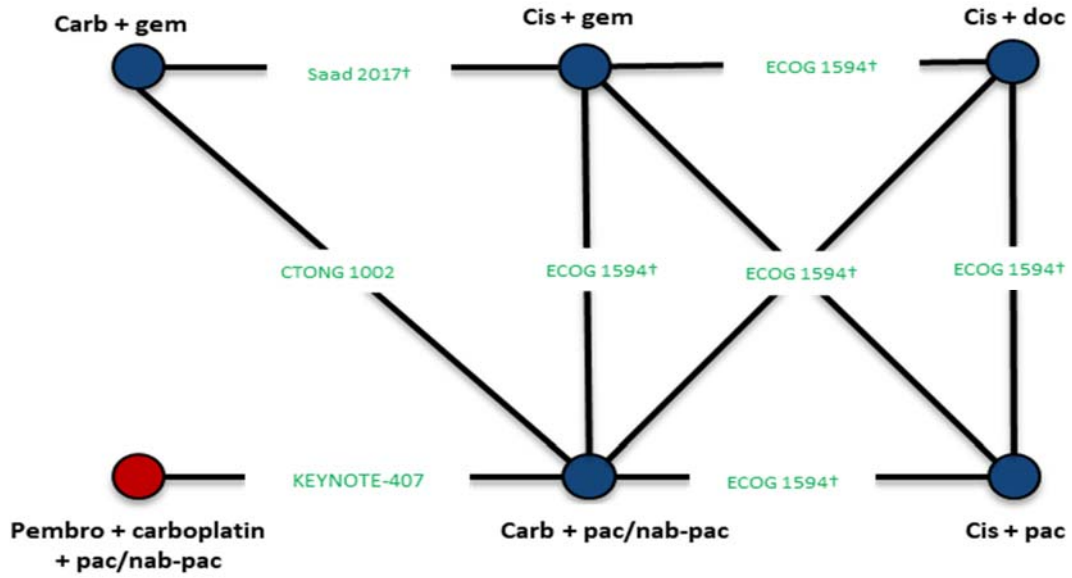


Table 34: Results of fixed effects network meta-analysis based on constant hazard ratio assumption; progression-free survival; squamous, PD-L1 unselected; results presented as hazard ratios between all competing interventions along with 95% credible intervals

Carb + gem	1.11 (0.78, 1.58)	0.99 (0.63, 1.58)	1.28 (0.88, 1.88)	0.85 (0.54, 1.34)	**1.98 (1.29, 3.03)**

0.90 (0.63, 1.29)	**Carb + pac or nab-pac**	0.90 (0.63, 1.29)	1.16 (0.83, 1.62)	0.77 (0.54, 1.09)	**1.79 (1.43, 2.23)**
1.01 (0.63, 1.59)	1.11 (0.78, 1.59)	**Cis + doc**	1.29 (0.89, 1.86)	0.85 (0.59, 1.23)	**1.99 (1.31, 3.03)**
0.78 (0.53, 1.14)	0.86 (0.62, 1.21)	0.77 (0.54, 1.12)	**Cis + gem**	**0.66 (0.46, 0.95)**	**1.54 (1.02, 2.31)**
1.18 (0.74, 1.86)	1.31 (0.91, 1.86)	1.17 (0.82, 1.69)	**1.51 (1.05, 2.18)**	**Cis + pac**	**2.33 (1.53, 3.55)**
0.51 (0.33, 0.77)	**0.56 (0.45, 0.70)**	**0.50 (0.33, 0.77)**	**0.65 (0.43, 0.98)**	**0.43 (0.28, 0.65)**	**Pembro + carb + pac or nab-pac**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 9.14; Deviance: 4.11

NMA 2: Unselected for histology, PD-L1 unselected

Overall survival

There were 23 trials evaluating 9 treatments included in the unselected for histology, PD-L1 unselected network (Figure 23) for overall survival. The network included trials that did not select patients based on histology status in addition to squamous-only trials. Trials included in this analysis were relatively homogenous with respect to study, treatment, and baseline patient characteristics such as ECOG performance status, disease stage, sex, and race/ethnicity. However, heterogeneity is introduced into this NMA as it included trials that did not select patients based upon histology status, a known treatment effect modifier. Therefore, meta-regression was performed with the proportion of non-squamous patients in each trial as a covariate which accounts for differences of the effect modifier between studies. The results of the fixed effects NMA is shown in Table 35 and random effects NMA is shown in Table 36. The random effects model is preferred (although the DIC for FE is lower [FE: 36.75 vs. RE: 37.56]) as it estimates between-study heterogeneity. Time-varying results for both fixed effects and random effects can be found in Appendix D1.2.3.1.

Based on the fixed effects NMA of the unselected for histology, PD-L1 unselected population, the point estimate of the HR for pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin versus all other interventions was less than one. Pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin was statistically superior to all competing interventions with HR point estimates ranging from 0.49 to 0.59. Additionally, cisplatin + docetaxel was statistically superior to carboplatin + docetaxel [HR: 0.82, 95% CrI: 0.72, 0.94] and cisplatin + docetaxel was statistically superior to cisplatin + vinorelbine [HR: 0.88, 95% CrI: 0.79, 0.98]. Similar results were observed based on the random effects NMA for the unselected for

histology, PD-L1 unselected population. Pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin HR point estimates versus all competing interventions was less than one and statistically superior to all competing interventions with the exception of carboplatin + vinorelbine. Platinum-based doublet regimens were not statistically different from one another under the random-effects constant HR model.

Analysis of the time-varying NMA fixed effects model show the HR for all interventions versus carboplatin + paclitaxel/nab-paclitaxel (anchor treatment) did not change over time. However, the HR for cisplatin + vinorelbine versus the anchor treatment increased over time in a statistically meaningful fashion. Analysis of the time-varying NMA random effects model showed the HR for all interventions, with the exception of cisplatin + vinorelbine, versus the anchor treatment did not change significantly over time. As the HR for the anchor treatment versus cisplatin + vinorelbine did vary over time, the NMA results assuming proportional hazards must be interpreted with caution for both fixed effects and random effects analyses with respect to OS in the unselected for histology, PD-L1 unselected population.

Figure 23: Network of evidence for overall survival; unselected for histology, PD-L1 unselected; hazard ratios

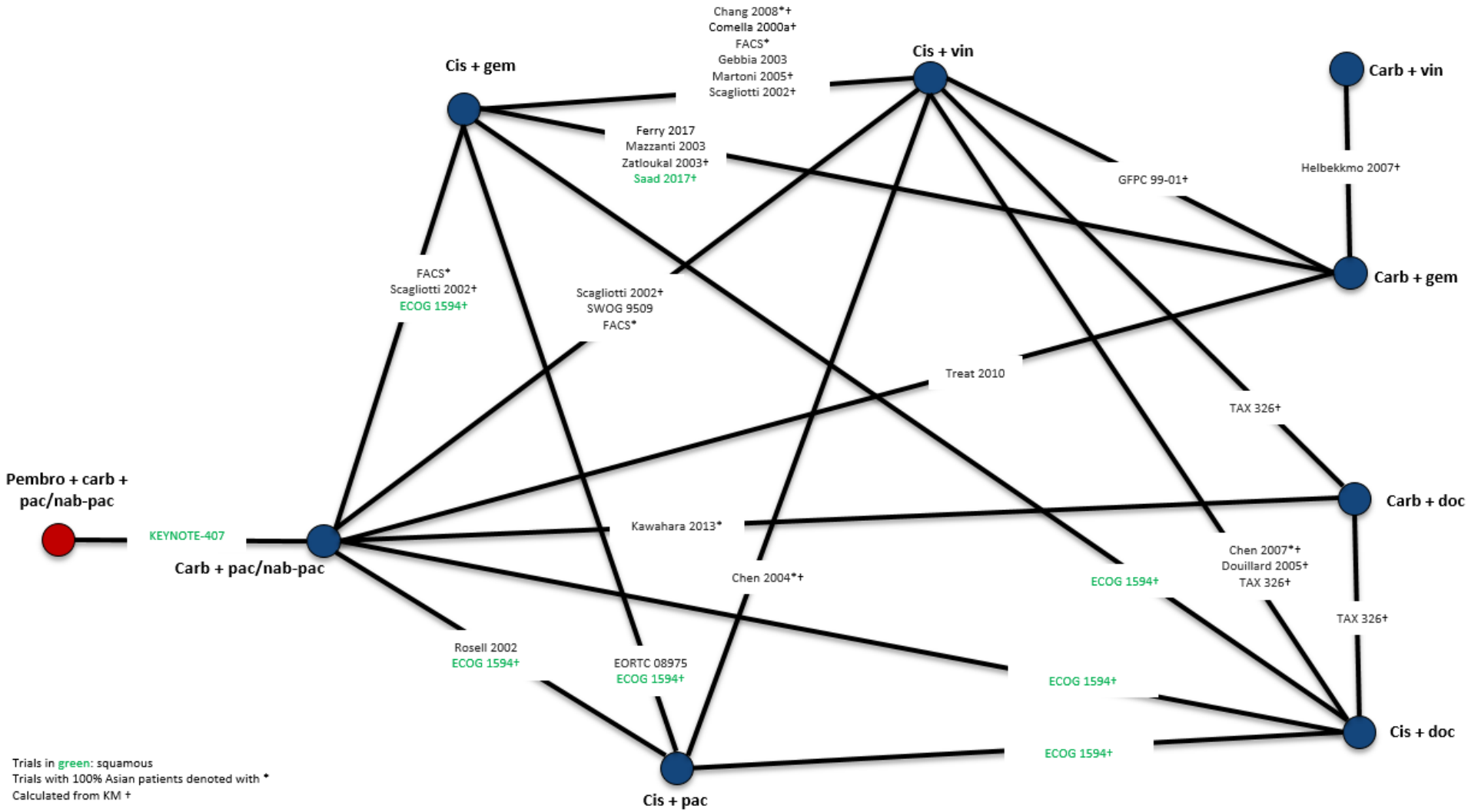


Table 35: Results of fixed effects network meta-analysis based on constant hazard ratio assumption; overall survival; unselected for histology, PD-L1 unselected; results presented as constant hazard ratios between all competing interventions along with 95% credible intervals with proportion squamous covariate

Carb + pac or nab-pac	0.93 (0.79, 1.10)	1.02 (0.87, 1.19)	1.04 (0.81, 1.33)	1.13 (0.98, 1.30)	1.09 (0.96, 1.24)	1.11 (0.99, 1.24)	0.99 (0.89, 1.10)	**1.90 (1.28, 2.79)**
1.08 (0.91, 1.27)	**Carb + doc**	1.10 (0.91, 1.33)	1.12 (0.85, 1.48)	**1.22 (1.06, 1.39)**	1.18 (0.99, 1.39)	1.20 (0.99, 1.44)	1.07 (0.93, 1.22)	**2.04 (1.33, 3.13)**
0.98 (0.84, 1.15)	0.91 (0.75, 1.10)	**Carb + gem**	1.02 (0.84, 1.24)	1.11 (0.93, 1.32)	1.07 (0.96, 1.19)	1.09 (0.92, 1.29)	0.97 (0.85, 1.12)	**1.86 (1.20, 2.85)**
0.96 (0.75, 1.24)	0.89 (0.68, 1.17)	0.98 (0.81, 1.19)	**Carb + vin**	1.08 (0.84, 1.40)	1.05 (0.84, 1.31)	1.07 (0.82, 1.38)	0.95 (0.75, 1.21)	**1.83 (1.13, 2.90)**
0.89 (0.77, 1.02)	**0.82 (0.72, 0.94)**	0.90 (0.76, 1.07)	0.92 (0.71, 1.20)	**Cis + doc**	0.97 (0.84, 1.12)	0.98 (0.84, 1.16)	**0.88 (0.79, 0.98)**	**1.68 (1.11, 2.56)**
0.92 (0.81, 1.04)	0.85 (0.72, 1.01)	0.94 (0.84, 1.04)	0.95 (0.76, 1.19)	1.04 (0.90, 1.20)	**Cis + gem**	1.02 (0.89, 1.17)	0.91 (0.82, 1.01)	**1.74 (1.14, 2.64)**
0.90 (0.80, 1.01)	0.84 (0.69, 1.01)	0.92 (0.78, 1.09)	0.94 (0.72, 1.21)	1.02 (0.86, 1.20)	0.98 (0.86, 1.13)	**Cis + pac**	0.89 (0.78, 1.02)	**1.71 (1.14, 2.55)**
1.01 (0.91, 1.12)	0.94 (0.82, 1.07)	1.03 (0.89, 1.18)	1.05 (0.82, 1.33)	**1.14 (1.02, 1.27)**	1.10 (0.99, 1.22)	1.12 (0.98, 1.28)	**Cis + vin**	**1.91 (1.26, 2.90)**
0.53 (0.36, 0.78)	**0.49 (0.32, 0.75)**	**0.54 (0.35, 0.83)**	**0.55 (0.34, 0.89)**	**0.59 (0.39, 0.90)**	**0.57 (0.38, 0.88)**	**0.59 (0.39, 0.88)**	**0.52 (0.34, 0.79)**	**Pembro + carb + pac or nab-pac**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 36.75; Deviance: 28.76

Table 36: Results of random effects network meta-analysis based on constant hazard ratio assumption; overall survival; unselected for histology, PD-L1 unselected; results presented as constant hazard ratios between all competing interventions along with 95% credible intervals with proportion squamous covariate

Carb + pac or nab-pac	0.92 (0.71, 1.17)	1.03 (0.85, 1.25)	1.05 (0.76, 1.47)	1.11 (0.91, 1.33)	1.10 (0.94, 1.28)	1.10 (0.91, 1.28)	0.99 (0.86, 1.13)	**1.76 (1.20, 2.59)**
1.09 (0.85, 1.40)	**Carb + doc**	1.12 (0.85, 1.48)	1.14 (0.78, 1.70)	1.20 (0.96, 1.50)	1.19 (0.94, 1.54)	1.19 (0.89, 1.56)	1.07 (0.86, 1.34)	**1.92 (1.20, 3.06)**
0.97 (0.80, 1.18)	0.90 (0.67, 1.18)	**Carb + gem**	1.02 (0.78, 1.34)	1.08 (0.85, 1.34)	1.07 (0.92, 1.24)	1.06 (0.84, 1.31)	0.96 (0.80, 1.15)	**1.71 (1.09, 2.64)**
0.95 (0.68, 1.32)	0.87 (0.59, 1.28)	0.98 (0.75, 1.28)	**Carb + vin**	1.05 (0.73, 1.48)	1.04 (0.77, 1.41)	1.04 (0.72, 1.45)	0.94 (0.68, 1.28)	1.67 (1.00, 2.80)
0.90 (0.75, 1.09)	0.83 (0.67, 1.04)	0.93 (0.75, 1.17)	0.95 (0.68, 1.37)	**Cis + doc**	0.99 (0.82, 1.20)	0.99 (0.79, 1.23)	0.89 (0.76, 1.04)	**1.59 (1.02, 2.49)**
0.91 (0.78, 1.06)	0.84 (0.65, 1.07)	0.94 (0.81, 1.09)	0.96 (0.71, 1.30)	1.01 (0.84, 1.22)	**Cis + gem**	1.00 (0.82, 1.18)	0.90 (0.79, 1.02)	**1.61 (1.05, 2.43)**
0.91 (0.78, 1.10)	0.84 (0.64, 1.12)	0.94 (0.76, 1.20)	0.96 (0.69, 1.39)	1.01 (0.82, 1.27)	1.00 (0.84, 1.22)	**Cis + pac**	0.91 (0.76, 1.10)	**1.61 (1.08, 2.43)**
1.01 (0.88, 1.16)	0.93 (0.74, 1.16)	1.04 (0.87, 1.25)	1.06 (0.78, 1.47)	1.12 (0.96, 1.31)	1.11 (0.98, 1.26)	1.10 (0.91, 1.32)	**Cis + vin**	**1.79 (1.17, 2.71)**
0.57 (0.39, 0.84)	**0.52 (0.33, 0.84)**	**0.58 (0.38, 0.92)**	0.60 (0.36, 1.00)	**0.63 (0.40, 0.98)**	**0.62 (0.41, 0.95)**	**0.62 (0.41, 0.93)**	**0.56 (0.37, 0.85)**	**Pembro + carb + pac or nab-pac**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 37.56; Deviance: 24.28; SD: 0.08

Progression-free survival

Eighteen trials evaluating 8 treatments were included in the unselected for histology, PD-L1 unselected network (Figure 24) for PFS. The unselected for histology (PD-L1 unselected) networks included trials that did not select patients based on histology status in addition to squamous-only trials. Trials included in this analysis were relatively homogenous with respect to study, treatment, and baseline patient characteristics such as ECOG performance status, disease stage, sex, and race/ethnicity. To deal with heterogeneity associated with inclusion of studies that did not select patients based upon histology, meta-regression was performed with the proportion of non-squamous patients in each trial as a covariate to account for differences of the effect modifier between studies. Results of the fixed effects NMA are shown in Table 37 and the random-effects NMA are shown in Table 38.The random effects model is preferred based upon the associated lower DIC and [FE: 32.21 vs. RE: 31.97] and more plausible assumptions regarding between-study heterogeneity. Time-varying results for both fixed effects and random effects can be found in Appendix D1.2.3.1.

Based on the fixed effects NMA of the unselected for histology, PD-L1 unselected population, the point estimate of the HR for pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin versus all other interventions was less than one. Pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin was statistically superior to all competing interventions (except carboplatin + docetaxel) with HR point estimates ranging from 0.51 to 0.60. Additionally, cisplatin + gemcitabine was statistically superior to carboplatin + gemcitabine [HR: 0.85, 95% CrI: 0.72, 1.00]. Similar results were observed based on the random effects NMA for the unselected for histology, PD-L1 unselected population. Pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin HR point estimates versus all competing interventions was less than one and statistically superior to all competing interventions, except carboplatin + docetaxel. Platinum-based doublet regimens were not statistically different from one another under the random-effects constant HR model.

Analysis of the time-varying NMA fixed effects model shows that the HR for most interventions, except carboplatin + docetaxel versus carboplatin + paclitaxel/nab-paclitaxel (anchor treatment), did not statistically change over time. Similarly, the time-varying random effects model shows that most interventions (except cisplatin + vinorelbine and carboplatin + docetaxel, versus the anchor treatment) did not change significantly over time, NMA results assuming proportional hazards must therefore be interpreted with caution for both fixed effects and random effects analyses with respect to PFS in the unselected for histology, PD-L1 unselected population.

Figure 24: Network of evidence for progression-free survival; unselected for histology, PD-L1 unselected; hazard ratios

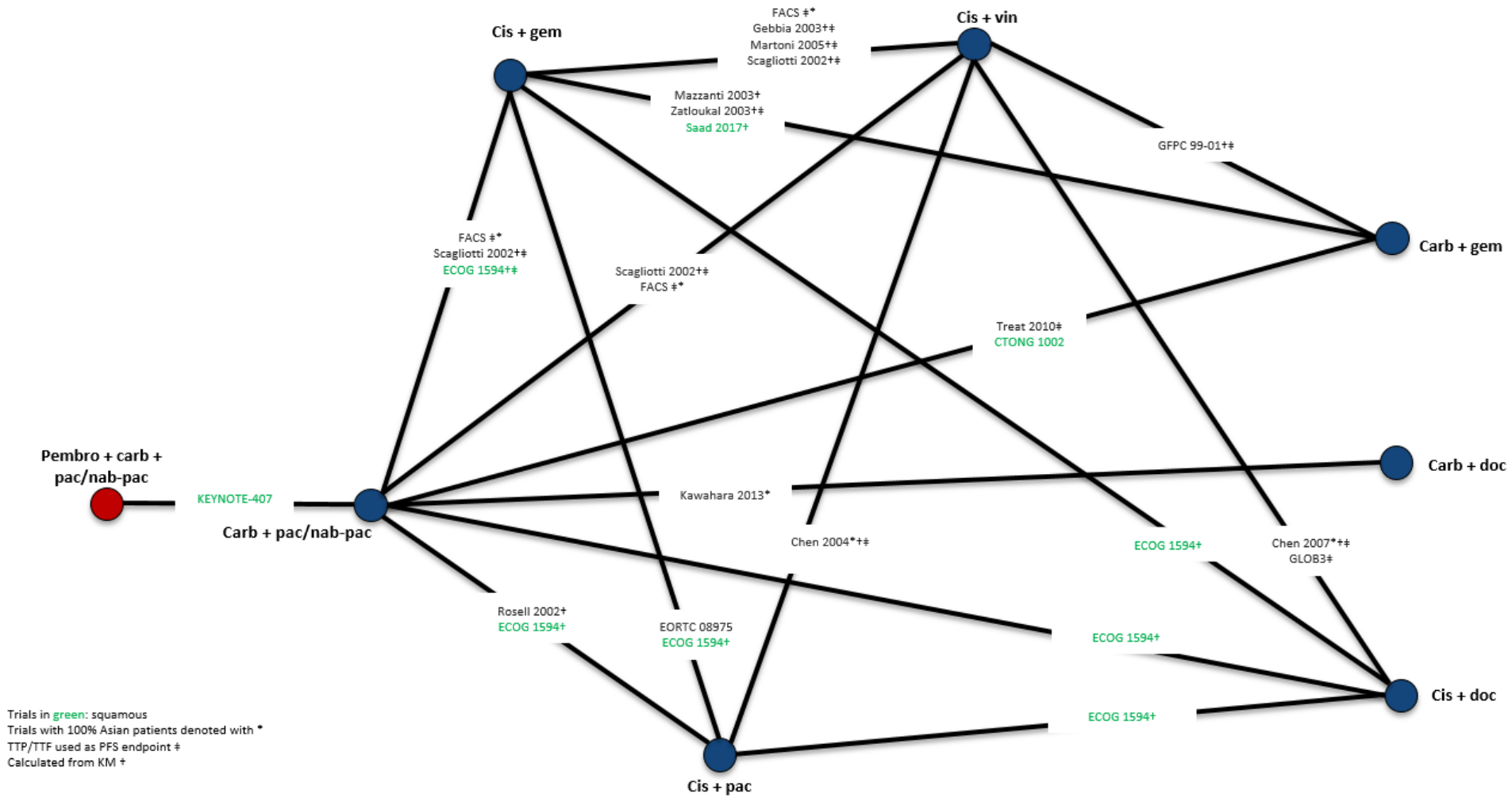


Table 37: Results of fixed effects network meta-analysis based on constant hazard ratio assumption; progression-free survival; unselected for histology, PD-L1 unselected; results presented as constant hazard ratios between all competing interventions along with 95% credible intervals with proportion non-squamous covariate

Carb + pac or nab-pac	1.18 (0.75, 1.86)	0.88 (0.74, 1.05)	0.98 (0.82, 1.18)	1.04 (0.91, 1.18)	0.96 (0.84, 1.09)	0.95 (0.84, 1.08)	**1.72 (1.28, 2.32)**
0.85 (0.54, 1.34)	**Carb + doc**	0.74 (0.46, 1.21)	0.83 (0.51, 1.36)	0.88 (0.55, 1.40)	0.81 (0.51, 1.31)	0.80 (0.51, 1.29)	1.45 (0.81, 2.58)
1.14 (0.95, 1.36)	1.35 (0.83, 2.19)	**Carb + gem**	1.12 (0.89, 1.41)	**1.18 (1.00, 1.40)**	1.09 (0.90, 1.33)	1.08 (0.91, 1.30)	**1.96 (1.38, 2.77)**
1.02 (0.85, 1.23)	1.21 (0.74, 1.97)	0.90 (0.71, 1.12)	**Cis + doc**	1.06 (0.88, 1.27)	0.98 (0.81, 1.19)	0.97 (0.83, 1.14)	**1.75 (1.23, 2.49)**
0.96 (0.85, 1.10)	1.14 (0.71, 1.81)	**0.85 (0.72, 1.00)**	0.94 (0.79, 1.13)	**Cis + gem**	0.92 (0.81, 1.06)	0.92 (0.82, 1.02)	**1.65 (1.18, 2.32)**
1.04 (0.92, 1.18)	1.24 (0.77, 1.97)	0.92 (0.75, 1.11)	1.02 (0.84, 1.24)	1.08 (0.94, 1.24)	**Cis + pac**	0.99 (0.86, 1.14)	**1.79 (1.28, 2.49)**
1.05 (0.93, 1.19)	1.24 (0.77, 1.98)	0.92 (0.77, 1.10)	1.03 (0.88, 1.21)	1.09 (0.98, 1.21)	1.01 (0.87, 1.16)	**Cis + vin**	**1.80 (1.28, 2.54)**
0.58 (0.43, 0.78)	0.69 (0.39, 1.23)	**0.51 (0.36, 0.73)**	**0.57 (0.40, 0.82)**	**0.60 (0.43, 0.85)**	**0.56 (0.40, 0.78)**	**0.55 (0.39, 0.78)**	**Pembro + carb + pac or nab-pac**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 32.21; Deviance: 25.21

Table 38: Results of random effects network meta-analysis based on constant hazard ratio assumption; progression-free survival; unselected for histology, PD-L1 unselected; results presented as constant hazard ratios between all competing interventions along with 95% credible intervals with proportion non-squamous covariate

Carb + pac or nab-pac	1.18 (0.70, 1.99)	0.87 (0.70, 1.08)	0.95 (0.72, 1.23)	1.02 (0.85, 1.21)	0.90 (0.71, 1.09)	0.94 (0.79, 1.14)	**1.75 (1.18, 2.57)**
0.85 (0.50, 1.43)	**Carb + doc**	0.74 (0.42, 1.31)	0.81 (0.44, 1.44)	0.87 (0.50, 1.50)	0.77 (0.42, 1.33)	0.80 (0.46, 1.38)	1.48 (0.75, 2.89)

1.14 (0.92, 1.43)	1.35 (0.77, 2.37)	**Carb + gem**	1.09 (0.80, 1.47)	1.17 (0.95, 1.43)	1.04 (0.77, 1.33)	1.08 (0.87, 1.35)	**2.00** **(1.27, 3.10)**
1.05 (0.81, 1.38)	1.24 (0.69, 2.26)	0.92 (0.68, 1.26)	**Cis + doc**	1.07 (0.84, 1.40)	0.95 (0.70, 1.25)	0.99 (0.80, 1.26)	**1.84** **(1.14, 2.95)**
0.98 (0.82, 1.17)	1.15 (0.67, 2.00)	0.85 (0.70, 1.05)	0.93 (0.72, 1.19)	**Cis + gem**	0.88 (0.70, 1.07)	0.93 (0.79, 1.09)	**1.71** **(1.11, 2.61)**
1.11 (0.92, 1.41)	1.31 (0.75, 2.35)	0.97 (0.75, 1.30)	1.06 (0.80, 1.42)	1.13 (0.94, 1.43)	**Cis + pac**	1.05 (0.85, 1.34)	**1.93** **(1.28, 3.04)**
1.06 (0.88, 1.27)	1.25 (0.72, 2.16)	0.92 (0.74, 1.15)	1.01 (0.79, 1.26)	1.08 (0.92, 1.26)	0.96 (0.75, 1.17)	**Cis + vin**	**1.85** **(1.19, 2.86)**
0.57 **(0.39, 0.85)**	0.68 (0.35, 1.33)	**0.50** **(0.32, 0.79)**	**0.54** **(0.34, 0.87)**	**0.58** **(0.38, 0.90)**	**0.52** **(0.33, 0.78)**	**0.54** **(0.35, 0.84)**	**Pembro + carb + pac or nab-pac**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.
DIC: 31.97; Deviance: 19.59; SD: 0.11

Discussion

The objective of the NMAs was to evaluate the comparative efficacy of pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin regimens versus competing interventions as well as estimate clinical efficacy between platinum-based doublet standard of care regimens used for the first-line treatment of metastatic squamous NSCLC patients. Data demonstrating the efficacy of pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin regimens was obtained from KEYNOTE-407. Networks of evidence were created for pure squamous histology and unselected for histology in conjunction with pure squamous histology patients (PD-L1 unselected). The squamous (PD-L1 unselected) network contained only trials conducted in exclusively squamous patients. Additionally, the unselected for histology (PD-L1 unselected) networks included trials that did not select patients based on histology status in addition to squamous-only trials. Therefore, meta-regression was employed in unselected for histology NMAs to estimate treatment effects in a squamous population as this was the population of interest. The primary outcomes for analysis were OS and PFS.

Overall, the results demonstrated that pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin is an effective treatment relative to alternative interventions for squamous NSCLC. Additionally, results suggested standard of care platinum doublet regimens are not statistically different from one another in squamous patients for both OS and PFS, with the exception of cisplatin + paclitaxel compared to cisplatin + gemcitabine.[41] Similar findings in relation to comparable efficacy across the SoC platinum doublets has also been reported in the published literature.[39]

NMAs were performed using both constant HRs and time-varying HRs based on KM curves. Preferred analyses were based on random effects models except for the pure squamous networks where the fixed effects model was used because a limited number of included trials precluded estimation of heterogeneity. The random effects model is more clinically plausible because it assumes that study and patient characteristics differ between trials and each study has its own true treatment effect. Although random effects models are generally more plausible, in cases where only one trial informs treatment comparisons (trials connecting treatments), heterogeneity is not estimable as seen in the pure squamous networks. However, trials included in the pure squamous networks have little heterogeneity with respect to possible treatment effect modifiers such as histology, ECOG performance status, disease stage, sex, and race/ethnicity. Therefore, fixed effects models used for the pure squamous NMAs have minimal risk of bias although between-study heterogeneity was inestimable using random effects.

NMAs were performed based on both hazard ratios and KM curves. NMA for survival outcomes based on HRs rely on the proportional hazards assumption, which is implausible if the hazard functions of competing interventions cross. A constant HR in the context of NMA implicitly assumes that the log hazard functions of all treatments in the network run parallel, which may be considered unrealistic. As an alternative to the constant HR, which is a univariate treatment effect measure, a multivariate treatment effect measure that describes how the relative treatment effect (e.g. HR) develops over time can be used. Ouwens et al and Jansen presented methods for NMA of survival data using a multi-dimensional or multivariate treatment effect as an alternative to the synthesis of one treatment effect (e.g. the constant HRs).[78, 79] The hazard functions of the interventions in a trial are modelled using known parametric survival functions, and the difference in the parameters are considered the multi-dimensional treatment effect, which are synthesized (and indirectly compared) across studies. With this approach, the treatment effects are represented by multiple parameters rather than a single parameter. By incorporating additional parameters for the treatment effect, the proportional hazards assumption is relaxed and the NMA model can be fitted more closely to the available data.

Results of the time-varying NMAs based on KM curves showed the HRs for most treatments did not change significantly with time. This suggests that the constant HR results provide the best combination of fit and parsimony for most treatments and scenarios. In unselected for histology, PD-L1 unselected networks, cisplatin + vinorelbine versus carboplatin + paclitaxel/nab-paclitaxel statistically varied over time with respect to OS. Similarly, both cisplatin + vinorelbine and carboplatin + docetaxel varied significantly over time with respect to PFS. Due to significant changes over time for cisplatin + vinorelbine and carboplatin + docetaxel, the proportional hazards assumption does not hold for these interventions in the unselected for histology, PD-L1 unselected population. For these cases, the results of the time-varying NMA are preferred.

The validity of the findings based on the current NMA depends on the quality of the RCTs and the extent of any violations in the similarity and consistency assumptions across studies. In a NMA of RCTs involving multiple treatment comparisons, the randomization holds only within the individual trials and not across trials. If the different direct comparisons show systematic differences in study and patient characteristics, and these differences are treatment effect modifiers, then the estimates of any indirect comparison as obtained with the NMA will be biased. The feasibility assessment to assess heterogeneity in terms of treatment and outcome characteristics as well as the study and patient characteristics was performed, which identified several important differences.

Although the studies were determined to be of good quality overall, most trials were open-label. Differences in terms of histology were accounted for by evaluating pure histology trials separately from trials that did not select based upon histology. Additionally, trial-level patient characteristics for histology were accounted for by incorporating a covariate of the proportion of squamous patients in the unselected for histology networks, as histology is a known treatment effect modifier. Finally, a number of trials were excluded from the NMA because they were outliers in potential relative treatment effect modifiers. Three trials (Ahmed et al., 2017[80], ECOG 1599[81], and Khodadad et al., 2014[82]) were removed from the unselected for histologies analysis because most enrolled patients had an ECOG performance status of 2, whereas other trials included mostly patients with ECOG scores of 0 or 1. Three trials (Chen et al., 2006[83], Kristensen et al., 2017[84], and NVALT-3[85]) were removed as they were conducted exclusively in elderly patients. Finally, both KEYNOTE-024[32, 33] and KEYNOTE-042[34] were removed from the analysis as pembrolizumab monotherapy is only indicated in high PD-L1 expressors (PD-L1 ≥ 50%) in the UK and the target population for analyses conducted were patients not selected by PD-L1 expression level. Following the removal of trials that were outliers for various potential relative treatment effect modifiers and the incorporation of a covariate to adjust for histology in the unselected for histology networks, the remaining trials in the analysis networks were deemed to be reasonably similar and differences in trial or patient characteristics were not considered likely to bias indirect comparison.

Given limited number of trials included in the squamous population analyses, there was insufficient data to estimate between-study heterogeneity reliably. Therefore, results for this outcome are based on fixed effects model. Mild to moderate heterogeneity that would usually be accounted for through random effects was not feasible; consequently, some of the credible intervals may be unrealistically narrow and should be interpreted with caution. Although heterogeneity is not able to be estimated by using random effects, the trials included in the pure squamous NMAs largely represented the target population with little variation with respect to treatment effect modifiers such as histology, ECOG performance status, and disease stage, thereby reducing risk of biased estimates. Finally, given the structure of the network for squamous analyses, comparisons to pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin, cisplatin + docetaxel, cisplatin + paclitaxel, and carboplatin + gemcitabine were mediated by multiple treatment comparisons, and were therefore more uncertain. This was also encountered among unselected for histology networks due to its star network structure.

As always, the SLR is also limited by using published data. There is a risk of publication bias as some clinical trials fail to be published while others are published only in abstract form, which present limited information. Our study included an extensive search of conference abstracts, which may have mitigated the impact on the results of the SLR, although posters or slides corresponding to the conference abstracts were not always available and often conferences do not provide complete information. Moreover, conference results should be interpreted with caution, as they do not undergo the same peer review process as fully published results. Finally, the search and selection were restricted to trials published in English. Therefore, there is a risk that non-English publications were not identified.

B.2.9.2 Pembrolizumab combination versus pembrolizumab monotherapy[42]

To estimate the treatment difference between pembrolizumab + carboplatin + nab/paclitaxel combination and pembrolizumab monotherapy, an ITC of OS and PFS outcomes was conducted, based on data from KEYNOTE-407 and KEYNOTE-042. No data were included from KEYNOTE-024 as the population of patients with squamous histology who received paclitaxel + carboplatin chemotherapy was very small (n=5).

The ITT population from both trials was used for the analysis of OS and PFS. All randomized subjects were included in the analyses according to the treatment group to which they were randomized.

Squamous and PD-L1 strong expression (TPS ≥50%) patients were selected from both studies. In order to have a common control arm to serve as anchor in the ITC, patients pre-assigned to paclitaxel + carboplatin chemotherapy from KEYNOTE-042 and KEYNOTE-407 and to nab-paclitaxel + carboplatin chemotherapy from KEYNOTE-407 were selected. Further exclusion criteria were applied to ensure complete similarity between the two study populations as follows:

- Patients with overall cancer stage III at screening were excluded from KEYNOTE-042 as KEYNOTE-407 already excluded these patients.
- Patients with untreated brain metastases were excluded from the study KEYNOTE-407 as KEYNOTE-042 already excluded these patients.

A summary of population selection is provided in Table 39.

Table 39: Summary of ITC population selection

Study identifier	Treatment arms	Population Selection	Patient numbers
KEYNOTE-407	- Pembrolizumab + Chemotherapy[a] - Chemotherapy[a]	Strong PD-L1 subjects (TPS ≥50%)	N=137 Pembro + chemo = 69 Chemo = 68
KEYNOTE-042	- Pembrolizumab - Chemotherapy[a]	Squamous histology subjects[b] Strong PD-L1 subjects (TPS ≥50%)	N=181 Pembro mono = 89 Chemo = 92
a: Paclitaxel and Carboplatin for KEYNOTE-042 and KEYNOTE-407 and Nab-paclitaxel and Carboplatin for KEYNOTE-407 b: KEYNOTE-407 only contains squamous subjects, so only those patients are selected from KEYNOTE-042.			

The relative treatment effect was measured by HR under the proportional hazard assumption. The ITC was performed using the Bucher method after adjusting populations and treatment arms using Inverse Probability of Treatment Weighting (IPTW).

Full details of the methodologies adopted in the ITC are presented in Appendix D1.2.3.2. In this section, we present the results of the OS and PFS analyses for the ITC. Details of the population adjustment by IPTW are provided in Appendix D1.2.3.2.

Overall survival

Table 40 presents the results of the ITC of pembrolizumab + chemotherapy vs. pembrolizumab monotherapy on OS after weighting through IPTW; the HR for the comparison is 0.97 (95% CI: 0.50, 1.89).

Progression-free survival

Table 41 presents the results of the ITC of pembrolizumab + chemotherapy vs. pembrolizumab monotherapy on PFS after weighting through IPTW; the HR for the comparison is 0.58 (95%CI: 0.33, 1.01).

Table 40: Analysis of OS (population adjusted by weighting; 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]
Overall Survival - population adjusted by weighting												
KEYNOTE-407[h]	69	22 (31.9)	Not Reached [11.3;-]				68	27 (39.7)	Not Reached [7.5;-]	0.58 [0.33;1.00]	0.97 [0.50;1.89]	0.922
KEYNOTE-042[i]				89	50 (56.2)	15.3 [11.9;31.7]	92	70 (76.1)	9.6 [8.1;11.7]	0.60 [0.41;0.88]		

a: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin

b: Number of patients: intention-to-treat

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

d: Based on weighted Cox regression model with treatment as a covariate stratified by taxane chemotherapy (Paclitaxel vs. Nab-paclitaxel) and geographic region (East Asia vs. non-East Asia) for KEYNOTE-407, and stratified by geographic region (East Asia vs. non-East Asia) and ECOG PS (0 vs. 1) for KEYNOTE-042.

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 (KEYNOTE-407) vs monotherapy (KEYNOTE-042)

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: ECOG PS (0 vs. 1), smoking status (never vs. former/current), age, gender, baseline tumour size. The derived weights were used in the Cox model to adjust for population imbalance across studies and treatment arms.

h: Database Cutoff Date: 03APR2018

i: Database Cutoff Date: 26FEB2018

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

Table 41: Analysis of PFS (population adjusted by weighting; 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: KEYNOTE-407[h]	69	37 (53.6)	8.0 [6.1;10.3]				68	51 (75.0)	4.2 [2.8;4.6]	0.35 [0.22;0.55]	0.58 [0.33;1.01]	0.055
Study: KEYNOTE-042[i]				89	71 (79.8)	6.9 [4.1;8.6]	92	78 (84.8)	6.1 [5.1;6.4]	0.61 [0.43;0.85]		

a: Paclitaxel and Carboplatin or Nab-paclitaxel and Carboplatin

b: Number of patients: intention-to-treat

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

d: Based on weighted Cox regression model with treatment as a covariate stratified by taxane chemotherapy (Paclitaxel vs. Nab-paclitaxel) and geographic region (East Asia vs. non-East Asia) for KEYNOTE-407, and stratified by geographic region (East Asia vs. non-East Asia) and ECOG PS (0 vs. 1) for KEYNOTE-042.

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 (KEYNOTE-407) vs monotherapy (KEYNOTE-042)

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: ECOG PS (0 vs. 1), smoking status (never vs. former/current), age, gender, baseline tumour size. The derived weights were used in the Cox model to adjust for population imbalance across studies and treatment arms.

h: Database Cutoff Date: 03APR2018

i: Database Cutoff Date: 26FEB2018

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

Discussion

There was a small numerical benefit in OS for pembrolizumab + chemotherapy over pembrolizumab monotherapy in metastatic, squamous NSCLC with PD-L1 TPS≥50%:

- Overall survival: hazard ratio = 0.97 (population-adjusted)

There was a larger numerical benefit in the same population in PFS for pembrolizumab + chemotherapy over pembrolizumab monotherapy in metastatic, squamous NSCLC, although the difference was not statistically significant:

- Progression-free survival: hazard ratio = 0.58 (population-adjusted) to 0.62 (unadjusted)

Confidence intervals around the estimated hazard ratios were wide due to the limited sample size in the individual trials (KN407 and KN042) as from both trials, only a subset of the patients was included in the indirect treatment comparison. This sub-setting was done to match the patient population in both trials and have a common control arm as anchor in the indirect treatment comparison.

Although the conducted indirect treatment comparison provides evidence of a numerical benefit for pembrolizumab + chemotherapy over pembrolizumab monotherapy, a head to head clinical trial would be required for definitive analysis comparing pembrolizumab + chemotherapy and pembrolizumab monotherapy.

B.2.10 Adverse reactions [15, 40]

In KEYNOTE-407, safety and tolerability were assessed by clinical and statistical review of all relevant parameters including adverse events (AEs) and laboratory test abnormalities during the treatment period up to the data cut-off date. Safety analyses were conducted in the ASaT population, which consisted of all randomised patients who received at least one dose of study treatment (n=558). Patients were included in the treatment group corresponding to the study treatment received. Incidence of, causality and outcome of AEs, Grade 3-5 AEs, Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AEOSI) were collected in the study. AEs were collected up to 30 days and SAEs up to 90 days after the last dose of study medication.

B.2.10.1 Extent of drug exposure

The duration of exposure (also referred to as Time on Treatment; ToT) was measured from the date of the first dose to the date of the last dose of treatment. Number of doses of study treatment was calculated from the number of administrations within the protocol regimen. The All Subjects as Treated (ASaT) population was used for extent of exposure analyses.

The ToT was longer for the pembrolizumab combination compared with the control (median duration of exposure: [redacted] days vs. [redacted] days, respectively). The mean number of treatment cycles received was [redacted] in the pembrolizumab combination and [redacted] in the control groups. (Table 42)

At the time of data cut-off, in the pembrolizumab combination, [redacted] of 278 patients ([redacted] person-years) had duration of exposure of ≥6 months compared with [redacted] of 280 patients ([redacted] person-years) in the control. [redacted] patients ([redacted] person-years) in the pembrolizumab combination group received treatment for over 12 months compared with [redacted] in the control ([redacted] person-years) (

Table 43).

In participants who received carboplatin/paclitaxel as chemotherapy, a slightly higher proportion in the pembrolizumab combination group completed all 4 cycles of carboplatin and paclitaxel compared with the control (Table 44). In the carboplatin/nab-paclitaxel treated population, similar proportions of participants in the pembrolizumab combination and the control completed the 4 cycles of carboplatin and 4 cycles (12 administrations) of nab-paclitaxel (Table 45). As expected, participants in the pembrolizumab combination group received more cycles of pembrolizumab compared with those in the control receiving the

placebo, indicating a longer duration on treatment. This was observed with both chemotherapy regimens.

Table 42: Summary of drug exposure (ASaT population)

	Pembrolizumab combination (N=278)	Control (N=280)
Number of Days on Therapy		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Number of Cycles		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Database Cut-off Date: 03APR2018		

Source: Clinical study report[4]

Table 43: Exposure by duration (ASaT population)

	Pembrolizumab combination (N=278)		Control (N=280)	
	n	Person-years	n	Person-years
Duration of Exposure				
> 0 m	[redacted]	[redacted]	[redacted]	[redacted]
>= 1 m	[redacted]	[redacted]	[redacted]	[redacted]
>= 3 m	[redacted]	[redacted]	[redacted]	[redacted]
>= 6 m	[redacted]	[redacted]	[redacted]	[redacted]
>= 12 m	[redacted]	[redacted]	[redacted]	[redacted]
Each subject is counted once on each applicable duration category row. Duration of Exposure is calculated as last dose date - first dose date + 1. Database Cut-off Date: 03APR2018				

Source: Clinical study report[4]

Table 44: Summary of drug administration by dose regimen (ASaT population - Carboplatin/Paclitaxel)

Number of Administrations	Pembrolizumab combination (N = 169)			Control (N = 167)		
	Pembrolizumab n (%)	Paclitaxel n (%)	Carboplatin n (%)	Placebo n (%)	Paclitaxel n (%)	Carboplatin n (%)
Subjects with at least one administration of the drug	169	169	169	167	167	167
1	8 (4.7)	9 (5.3)	8 (4.7)	12 (7.2)	13 (7.8)	12 (7.2)
2	10 (5.9)	12 (7.1)	11 (6.5)	19 (11.4)	21 (12.6)	19 (11.4)
3	7 (4.1)	15 (8.9)	12 (7.1)	9 (5.4)	14 (8.4)	14 (8.4)
4	10 (5.9)	133 (78.7)	138 (81.7)	16 (9.6)	119 (71.3)	122 (73.1)
>=5	134 (79.3)	0 (0.00)	0 (0.00)	111 (66.5)	0 (0.00)	0 (0.00)
Mean	9.6	3.6	3.7	7.5	3.4	3.5
SD	5.9	0.8	0.8	5.3	1.0	1.0
Median	8.0	4.0	4.0	7.0	4.0	4.0
Range	1 to 27	1 to 4	1 to 4	1 to 27	1 to 4	1 to 4
For subjects who crossed over to pembrolizumab from the Control Group, doses administered after crossover are excluded. Subjects with at least one administration of the drug will be taken as the denominator. The maximum allowed number of administrations for carboplatin and paclitaxel is 4. Database Cutoff Date: 03APR2018						

Source: Clinical study report[4]

Table 45: Summary of drug administration by dose regimen (ASaT population - Carboplatin/Nab-Paclitaxel)

Number of Administrations	Pembrolizumab combination (N = 109)			Control (N = 113)		
	Pembrolizumab n (%)	Nab-Paclitaxel n (%)	Carboplatin n (%)	Placebo n (%)	Nab-Paclitaxel n (%)	Carboplatin n (%)
Subjects with at least one administration of the drug	109	109	109	113	113	113
1	12 (11.0)	5 (4.6)	10 (9.2)	9 (8.0)	4 (3.5)	10 (8.8)
2	4 (3.7)	5 (4.6)	4 (3.7)	5 (4.4)	6 (5.3)	8 (7.1)
3	8 (7.3)	0 (0.00)	14 (12.8)	11 (9.7)	2 (1.8)	12 (10.6)
4	5 (4.6)	2 (1.8)	81 (74.3)	10 (8.8)	4 (3.5)	83 (73.5)
5-11	49 (45.0)	72 (66.1)	0 (0.00)	63 (55.8)	73 (64.6)	0 (0.00)
>=12	31 (28.4)	25 (22.9)	0 (0.00)	15 (13.3)	24 (21.2)	0 (0.00)
Mean	8.8	9.0	3.5	7.0	8.7	3.5
SD	5.8	3.1	0.9	4.5	3.2	1.0
Median	8.0	10.0	4.0	6.0	10.0	4.0
Range	1 to 25	1 to 12	1 to 4	1 to 23	1 to 12	1 to 4

For subjects who crossed over to pembrolizumab from the Control Group, doses administered after crossover are excluded.
Subjects with at least one administration of the drug will be taken as the denominator.
The maximum allowed number of administrations for carboplatin is 4. The maximum allowed number of administrations for nab-paclitaxel is 12.
Database Cutoff Date: 03APR2018

Source: Clinical study report[4]

B.2.10.2 Summary of adverse reactions[4, 35]

As detailed above, the duration of exposure was longer for participants in the pembrolizumab combination compared with the control, resulting in a prolonged time frame during which AEs could be collected in the pembrolizumab combination group. Nonetheless, the AE summary profiles observed in both the pembrolizumab combination and control arms in this study were generally consistent with the known safety profiles of the respective therapies administered. (Table 46)

Comparable proportions of patients in the pembrolizumab combination and control experienced AEs (98.2% vs 97.9%), Grade 3-5 AEs (69.8% vs 68.2%) and SAEs ([redacted] % vs [redacted] %). Drug-related AEs ([redacted] % vs [redacted] %), drug-related Grade 3 to 5 AEs ([redacted] % vs [redacted] %) and drug-related SAEs ([redacted] % vs [redacted] %) were observed more frequently with pembrolizumab combination than control, possibly due to the longer duration of exposure in the pembrolizumab combination group.

Higher rates of discontinuation of any drug within the treatment regimen due to an AE occurred in the pembrolizumab combination compared with the control (23.4% vs 11.8%), which was primarily driven by a higher rate of discontinuation of pembrolizumab (17.3%) compared with placebo (7.9%). Similar trends were also observed in discontinuations due to drug-related AE, serious AE, and serious drug-related AE. The differences in discontinuation rates between the treatment groups may be attributable to the longer duration of exposure in the pembrolizumab combination. Patients in the control were more likely to discontinue treatment for PD.

Discontinuation of all drugs due to an AE was relatively low in both treatment groups ([redacted] % in the pembrolizumab combination and [redacted] % in the control). Similar trends were observed in exposure-adjusted analyses of drug discontinuations.

AEs that led to death occurred in 23 (8.3%) of patients in the pembrolizumab combination group and in 18 (6.4%) patients in the control. The proportion of deaths considered by a trial investigator to be attributed to a drug-related AE was 3.6% in the pembrolizumab combination group compared with 2.1% in the control.

Table 46: Adverse reactions summary (ASaT population)

	Pembrolizumab combination		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	273	(98.2)	274	(97.9)
with no adverse event	5	(1.8)	6	(2.1)
with drug-related† adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	194	(69.8)	191	(68.2)
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	23	(8.3)	18	(6.4)
who died due to a drug-related adverse event	10	(3.6)	6	(2.1)
discontinued any drug due to an adverse event	65	(23.4)	33	(11.8)
discontinued pembrolizumab or placebo	48	(17.3)	22	(7.9)
discontinued any chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
discontinued all drugs	[redacted]	[redacted]	[redacted]	[redacted]
discontinued any drug due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued pembrolizumab or placebo	[redacted]	[redacted]	[redacted]	[redacted]
discontinued any chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
discontinued all drugs	[redacted]	[redacted]	[redacted]	[redacted]
discontinued any drug due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued pembrolizumab or placebo	[redacted]	[redacted]	[redacted]	[redacted]
discontinued any chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
discontinued all drugs	[redacted]	[redacted]	[redacted]	[redacted]
discontinued any drug due to a serious drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued pembrolizumab or placebo	[redacted]	[redacted]	[redacted]	[redacted]
discontinued any chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
discontinued all drugs	[redacted]	[redacted]	[redacted]	[redacted]

† Determined by the investigator to be related to the drug.

For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA 20.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Grades are based on NCI CTCAE version 4.03.

Database Cutoff Date: 03APR2018

Source: Clinical study report[4]

B.2.10.3 Adverse events[4, 35]

Overview of adverse events

The most frequently reported AEs were anaemia (pembrolizumab combination: 53.2%; control: 51.8%), alopecia (pembrolizumab combination: 46.0%; control: 36.4%), neutropenia (pembrolizumab combination: 37.8%; control: 32.9%) and nausea (pembrolizumab combination: 35.6%; control: 32.1%). (Table 47) The most frequently reported AEs (incidence ≥30%) in both treatment groups were among those typically associated with chemotherapy.

Certain AEs were observed at higher rates in the pembrolizumab combination group compared to the control (alopecia, thrombocytopenia, arthralgia, and pruritus). These differences were not observed in exposure-adjusted analyses, and may be associated with longer treatment duration in the pembrolizumab combination group.

The majority of AEs were grade 3 or lower and occurred in the first 3 months in the 2 treatment groups, as might be expected given that the chemotherapy components were administered during the first 4 cycles of treatment.

Table 47: Patients with adverse events by decreasing incidence (Incidence≥10% in one or more treatment groups; ASaT population)

	Pembrolizumab combination		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
Subjects with				
Anaemia	148	(53.2)	145	(51.8)
Alopecia	128	(46.0)	102	(36.4)
Neutropenia	105	(37.8)	92	(32.9)
Nausea	99	(35.6)	90	(32.1)
Thrombocytopenia	85	(30.6)	65	(23.2)
Diarrhoea	83	(29.9)	65	(23.2)
Decreased appetite	68	(24.5)	82	(29.3)
Constipation	64	(23.0)	61	(21.8)
Fatigue	63	(22.7)	72	(25.7)
Asthenia	60	(21.6)	59	(21.1)
Arthralgia	57	(20.5)	40	(14.3)
Neuropathy peripheral	57	(20.5)	45	(16.1)

	Pembrolizumab combination		Control	
	n	(%)	n	(%)
Vomiting	45	(16.2)	33	(11.8)
Rash	39	(14.0)	28	(10.0)
Cough	37	(13.3)	47	(16.8)
Myalgia	37	(13.3)	35	(12.5)
Dyspnoea	36	(12.9)	45	(16.1)
Pruritus	36	(12.9)	21	(7.5)
Pyrexia	34	(12.2)	37	(13.2)
Peripheral sensory neuropathy	32	(11.5)	36	(12.9)
White blood cell count decreased	31	(11.2)	30	(10.7)
Insomnia	28	(10.1)	23	(8.2)
Weight decreased	28	(10.1)	21	(7.5)
Haemoptysis	25	(9.0)	30	(10.7)
Neutrophil count decreased	24	(8.6)	28	(10.0)
Source: Clinical study report[4]				

Drug-related AEs

The incidence of drug-related AEs as determined by the investigator was 95.8% vs 88.9% for the pembrolizumab combination and control groups, respectively. The drug-related AEs were generally consistent with the known safety profiles of either pembrolizumab monotherapy or carboplatin/paclitaxel (or nab-paclitaxel).

The most frequently reported drug-related AEs (incidence ≥30%) were alopecia (pembrolizumab combination: [redacted] %; control: [redacted] %), anaemia (pembrolizumab combination: [redacted] %; control: [redacted] %), neutropenia (pembrolizumab combination: [redacted] %; control: [redacted] %) and nausea (pembrolizumab combination: [redacted] %; control: [redacted] %).(Table 48)

Table 48: Subjects with drug-related AEs by decreasing incidence (Incidence ≥10% in one of more treatment groups; ASaT population)

	Pembrolizumab combination		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab combination		Control	
	n	(%)	n	(%)
Alopecia	[redacted]			
Anaemia				
Neutropenia				
Nausea				
Thrombocytopenia				
Diarrhoea				
Neuropathy peripheral				
Fatigue				
Decreased appetite				
Asthenia				
Arthralgia				
Vomiting				
Myalgia				
Constipation				
Peripheral sensory neuropathy				
White blood cell count decreased				
Pruritus				
Rash				
Neutrophil count decreased				

Source: Clinical study report[4]

Grade 3 to 5 AEs

The incidences of Grade 3 to 5 AEs were similar in the pembrolizumab combination group (69.8%) compared with the control (68.2%). The most frequently reported Grade 3 to 5 AEs observed for participants treated with the pembrolizumab combination in this study were generally consistent with the known safety profiles of either pembrolizumab monotherapy or carboplatin/paclitaxel (or nab-paclitaxel).

The most frequently reported Grade 3 to 5 AEs (incidence ≥1 %) in both treatment groups were neutropenia (pembrolizumab combination: 22.7%; control: 24.6%) and anaemia (pembrolizumab combination: 15.5%; control: 20.4%), which are events typically associated with chemotherapy.

The incidence of Grade 3 to 5 AEs was generally comparable between the 2 groups, except pneumonitis (pembrolizumab combination: 2.5%; control: 0.4%), and autoimmune hepatitis (pembrolizumab combination: 1.8%; control: 0%), which occurred more frequently in the pembrolizumab combination group than control.

Table 49: Grade 3-5 AEs by decreasing incidence (Incidence ≥1% in one or more treatment groups; ASaT population)

	Pembrolizumab combination		Control	
	Number (%) of patients with at least one episode		Number (%) of patients with at least one episode	
Any type of adverse event	194	(69.8)	191	(68.2)
Specific adverse event				
Neutropenia	63	(22.7)	69	(24.6)
Anaemia	43	(15.5)	57	(20.4)
Thrombocytopenia	19	(6.8)	18	(6.4)
Pneumonia	18	(6.5)	17	(6.1)
Neutrophil count decreased	17	(6.1)	24	(8.6)
Febrile neutropenia	15	(5.4)	11	(3.9)
Leukopenia	13	(4.7)	12	(4.3)
White blood cell count decreased	12	(4.3)	11	(3.9)
Diarrhoea	11	(4.0)	6	(2.1)
Hyponatraemia	10	(3.6)	5	(1.8)
Fatigue	9	(3.2)	11	(3.9)
Pneumonitis	7	(2.5)	1	(0.4)
Asthenia	6	(2.2)	10	(3.6)
Colitis	6	(2.2)	2	(0.7)
Decreased appetite	6	(2.2)	5	(1.8)
Autoimmune hepatitis	5	(1.8)	0	(0.0)
Hyperkalaemia	5	(1.8)	4	(1.4)
Hypertension	5	(1.8)	5	(1.8)
Hypotension	5	(1.8)	5	(1.8)
Lung infection	5	(1.8)	3	(1.1)
Platelet count decreased	5	(1.8)	7	(2.5)
Arthralgia	4	(1.4)	2	(0.7)
Death	4	(1.4)	3	(1.1)
Dyspnoea	4	(1.4)	3	(1.1)
Haemoptysis	4	(1.4)	3	(1.1)
Pleural effusion	4	(1.4)	3	(1.1)
Sepsis	4	(1.4)	3	(1.1)
Syncope	4	(1.4)	3	(1.1)
Acute kidney injury	3	(1.1)	5	(1.8)
Gamma-glutamyltransferase increased	3	(1.1)	4	(1.4)
Hypokalaemia	3	(1.1)	1	(0.4)
Infusion related reaction	3	(1.1)	1	(0.4)
Nausea	3	(1.1)	4	(1.4)
Neuropathy peripheral	3	(1.1)	2	(0.7)
Pulmonary embolism	3	(1.1)	4	(1.4)

	Pembrolizumab combination		Control	
	Number (%) of patients with at least one episode		Number (%) of patients with at least one episode	
Pulmonary haemorrhage	3	(1.1)	1	(0.4)
Pyrexia	3	(1.1)	3	(1.1)
Respiratory failure	3	(1.1)	0	(0.0)
Aspartate aminotransferase increased	2	(0.7)	3	(1.1)
Back pain	2	(0.7)	5	(1.8)
Constipation	2	(0.7)	3	(1.1)
Cough	2	(0.7)	3	(1.1)
Hypercalcaemia	2	(0.7)	5	(1.8)
Hypophosphataemia	2	(0.7)	3	(1.1)
Lymphocyte count decreased	2	(0.7)	3	(1.1)
Alopecia	1	(0.4)	3	(1.1)
Hypomagnesaemia	1	(0.4)	4	(1.4)
Septic shock	1	(0.4)	3	(1.1)
Vomiting	1	(0.4)	6	(2.1)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA 20.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 03APR2018

Source: Clinical study report[4]

Drug-related grade 3 to 5 AEs

A similar percentage of patients in each treatment group reported drug-related Grade 3 to 5 AEs (pembrolizumab combination: [redacted] %; control: [redacted] %). The most frequently reported drug-related Grade 3 to 5 AEs were neutropenia (pembrolizumab combination: [redacted] %; control: [redacted] %) and anaemia (pembrolizumab combination: [redacted] %; control: [redacted] %), known AEs associated with chemotherapy. Rates of drug-related AEs were similar between the 2 groups. Although the incidences were low, drug-related Grade 3 to 5 autoimmune hepatitis and pneumonitis, known immune-related AEs associated with pembrolizumab, were each reported in [redacted] ([redacted] %) participants in the pembrolizumab combination and [redacted] in the control. (Table 50)

Table 50:Drug-related grade 3-5 AEs by system organ class and preferred term (Incidence ≥1% in one or more treatment group; ASaT population)

	Pembrolizumab combination		Control	
	Number (%) of patients with at least one episode		Number (%) of patients with at least one episode	
Subjects in population	278		280	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Specific event				
Blood and lymphatic system				
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal				
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
General				
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary				
Autoimmune hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations				
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural				
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]
Investigations				
Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nurtrition				
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system				
Neuropathy peripheral	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab combination		Control	
	Number (%) of patients with at least one episode		Number (%) of patients with at least one episode	
Renal and urinary				
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, mediastinal				
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue				
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]
Vascular				
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA 20.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 03APR2018

Source: Clinical study report[4]

B.2.10.4 Serious adverse events[4]

Overall serious adverse events

The serious adverse events (SAEs) observed in both treatment groups were generally consistent with the known safety profiles of pembrolizumab monotherapy or carboplatin/paclitaxel (or nab-paclitaxel) and were reported with similar frequencies.

The incidence of the most frequently reported SAEs (incidence ≥1% in either treatment group) were generally comparable between the 2 groups, except colitis, which was higher in the pembrolizumab combination group (pembrolizumab combination: [redacted] %; control: [redacted] %), and hypercalcemia, which was higher in the control group (pembrolizumab combination: [redacted] % control: [redacted] %). Colitis is a known immune AE associated with pembrolizumab, and hypercalcemia is known to be associated with squamous NSCLC.

The most frequently reported SAEs (incidence ≥2% in either treatment group) were pneumonia (pembrolizumab combination: [redacted] %; control: [redacted] %), febrile neutropenia (pembrolizumab combination: [redacted] %; control: [redacted] %), diarrhoea (pembrolizumab

combination: [redacted] %; control: [redacted] %), anaemia (pembrolizumab combination: [redacted] %; control: [redacted] %), pneumonitis (pembrolizumab combination: [redacted] %; control: [redacted] %), colitis (pembrolizumab combination: [redacted] %; control: [redacted] %), and pyrexia (pembrolizumab combination: [redacted] %; control: [redacted] %). (Table 51)

Table 51: SAEs by decreasing incidence (Incidence ≥1% in one or more treatment group; ASaT population)

	Pembrolizumab combination		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Haemoptysis	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]
Hypercalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

	Pembrolizumab combination		Control	
	n	(%)	n	(%)
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded. Serious adverse events up to 90 days of last dose are included. MedDRA 20.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Database Cutoff Date: 03APR2018				

Source: Clinical study report[4]

Drug-related SAEs

The overall incidence of drug-related SAEs was 25.2% for the pembrolizumab combination group and 18.2% for the control group. The most frequently reported drug-related SAE in both treatment groups was febrile neutropenia, which is an event typically associated with chemotherapy. The rates of drug-related febrile neutropenia SAEs were low (≤5%) and similar between the 2 groups and were generally consistent with the known safety profile of carboplatin /paclitaxel (or nab-paclitaxel). (Table 52)

Table 52: Drug-related SAEs by decreasing incidence (Incidence ≥1% in one or more treatment group; ASaT population)

	Pembrolizumab combination		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	70	(25.2)	51	(18.2)
with no adverse events	208	(74.8)	229	(81.8)
Febrile neutropenia	14	(5.0)	9	(3.2)
Pneumonia	7	(2.5)	3	(1.1)
Colitis	6	(2.2)	1	(0.4)
Anaemia	5	(1.8)	5	(1.8)
Pneumonitis	5	(1.8)	1	(0.4)
Thrombocytopenia	5	(1.8)	3	(1.1)
Diarrhoea	4	(1.4)	4	(1.4)
Infusion related reaction	4	(1.4)	1	(0.4)
Neutropenia	4	(1.4)	7	(2.5)
Sepsis	4	(1.4)	0	(0.0)
Leukopenia	3	(1.1)	0	(0.0)
Neutrophil count decreased	3	(1.1)	1	(0.4)
Pyrexia	3	(1.1)	0	(0.0)

Acute kidney injury	1	(0.4)	3	(1.1)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded.
Serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 03APR2018

Source: Clinical study report[4]

Deaths due to adverse events

There were 41 deaths due to an AE during the trial; 23 in the pembrolizumab combination group and 18 in the control group; 16 deaths (10 in the pembrolizumab combination group and 6 in the control group) were considered by the investigator to be related to the study treatment. In the pembrolizumab combination group, drug-related AEs resulting in death included respiratory failure, pneumonitis, sepsis, necrotizing fasciitis, hepatic failure, pulmonary haemorrhage, and death.

B.2.10.5 Adverse events of special interest

The incidence of AEOSIs was higher in the pembrolizumab combination group (28.8%) than the control (8.6%). The most frequent AEOSIs (>5%) in the pembrolizumab combination were hypothyroidism (7.9%), hyperthyroidism (7.2%), and pneumonitis (6.5%). (Table 53)

The incidence of AEOSIs in the pembrolizumab combination group was consistent with that seen in patients with lung cancer treated with pembrolizumab monotherapy; these AEs were not exacerbated by the addition of carboplatin/paclitaxel (or nab-paclitaxel) in the pembrolizumab combination group.

The majority of participants with AEOSIs in the pembrolizumab combination group experienced events with a maximum toxicity of Grade 1 or 2 ([redacted] participants [[redacted] %]); an additional [redacted] participants ([redacted] %) had Grade 3 AEOSIs, and [redacted] ([redacted] %) had Grade 4 AEOSIs that included colitis, autoimmune hepatitis, hypophysitis, and infusion reaction. Serious AEOSIs were relatively infrequent, occurring in [redacted] % of participants in the pembrolizumab combination group. There were 2 deaths due to pneumonitis, 1 in the pembrolizumab combination and 1 in the control.

Table 53: AEOSIs by category (ASaT population)

	Pembrolizumab combination		Control	
	n	(%)	n	(%)
Subjects in population	278		280	
with one or more adverse events	80	(28.8)	24	(8.6)
with no adverse events	198	(71.2)	256	(91.4)
Colitis	7	(2.5)	4	(1.4)
Hepatitis	5	(1.8)	0	(0.0)
Hyperthyroidism	20	(7.2)	2	(0.7)
Hypophysitis	3	(1.1)	0	(0.0)
Hypothyroidism	22	(7.9)	5	(1.8)
Infusion Reactions	8	(2.9)	6	(2.1)
Nephritis	2	(0.7)	2	(0.7)
Pneumonitis	18	(6.5)	6	(2.1)
Severe Skin Reactions	5	(1.8)	1	(0.4)
Thyroiditis	3	(1.1)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A bolded term appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database Cutoff Date: 03APR2018

Source: Clinical study report[4]

B.2.11 Ongoing studies

Results provided in this submission are from IA2 of the KEYNOTE-407 clinical trial, based on data cut-off date of 3 April 2018. As described in Section B.2.4, the timing of further analyses is event-drive, with final analysis of the study schedules after approximately 361 death events are observed. The final analysis is currently estimated in [redacted].

B.2.12 Innovation

Pembrolizumab, a monoclonal antibody, directly blocks the interaction of PD-1 and its ligands PD-L1 and PD-L2 enabling the immune response of both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and anti-tumour immunity. At present, patients with squamous NSCLC have more limited treatment options than those other histologies, and typically have poorer prognosis. Currently, first line treatment with pembrolizumab for patients with squamous NSCLC is limited to those whose tumours have high levels of PD-L1 expression (TPS ≥50%).[86] The clinical efficacy and safety data presented in this submission show that pembrolizumab, when combined with chemotherapy, offers a durable benefit in PFS and OS for all squamous NSCLC patients, regardless of PD-L1 expression levels, with an acceptable tolerability profile. [4, 35]

B.2.13 Interpretation of clinical effectiveness and safety evidence

The safety and efficacy data from IA2 of KEYNOTE-407, as presented in this submission, are robust and demonstrate substantial, clinically meaningful benefit of pembrolizumab combination compared with chemotherapy control for all efficacy endpoints in previously untreated patients with squamous NSCLC. In addition, the safety results from the study are largely consistent with the established safety profile of pembrolizumab plus carboplatin plus nab/paclitaxel, and affirm an acceptable tolerability profile in the target population.

The key findings from the study are summarised below.

Pembrolizumab combination significantly prolongs OS and PFS and results in higher ORR and longer duration of response with similar time to response compared with current chemotherapy SOC

After median follow-up of 7.8 months, first line treatment with pembrolizumab combination significantly improved OS (HR=0.64; 95% CI: 0.49, 0.85; p=0.0008) and PFS (HR=0.56; 95% CI: 0.45, 0.70; p<0.0001) compared with chemotherapy control in patients with metastatic squamous NSCLC, regardless of PD-L1 expression levels.

Median OS was longer in the pembrolizumab combination compared with the control (15.9 months vs 11.3 months). Similarly, median PFS was also longer in the pembrolizumab combination group than the control (6.4 months vs 4.8 months). The Kaplan-Meier curves for both OS and PFS separated early and continued over time. Improvements in OS and PFS

were observed in all PD-L1 subgroups, with an incremental benefit observed with increased PD-L1 expression.

Pembrolizumab combination provided a statistically significant improvement in confirmed ORR relative to control (57.9% vs 38.4%), representing a 19.5% difference (p<0.0001) between the two treatment groups driven primarily by greater levels of partial response (PR) in the pembrolizumab combination compared with control (56.5% vs 36.3%). The median duration of response in the pembrolizumab combination group was longer that in the control (7.7 months vs 4.8 months) and more participants had extended responses for ≥6 months ([redacted] % vs [redacted] %) and ≥9 months ([redacted] % vs [redacted] %) by KM estimation. The median time to response was 1.4 months in both treatment groups.

Pembrolizumab combination treatment effect on OS, PFS and OR was observed in all subgroups assessed and regardless of PD-L1 expression levels

The benefit of pembrolizumab combination treatment over control was reported in all subgroup analyses, including age, gender, geographic region, performance status, taxane chemotherapy option and PD-L1 expression levels.

HRQoL was improved in pembrolizumab combination patients while patients in the chemo control group experienced deteriorating HRQoL

The addition of pembrolizumab to chemotherapy regimen did not affect HRQoL during the period patients received chemotherapy (based on week 9 assessments). Once chemotherapy cycles were completed (week 18 assessments), patients in the pembrolizumab combination group showed a slight increase over baseline in HRQoL scores while the control group showed a slight decrease, resulting in a statistically significant improvement in HRQoL in the pembrolizumab combination relative to control significant (LS Means [redacted]; 95% CI [redacted], p=[redacted]).

Pembrolizumab combination has an acceptable tolerability profile which is consistent with the known safety profiles of the therapies administered

The duration of exposure was longer for participants in the pembrolizumab combination compared with the control, resulting in a prolonged time frame during which AEs could be collected in the pembrolizumab combination group. Nonetheless, the AE summary profiles

observed in both the pembrolizumab combination and control arms were generally consistent with the known safety profiles of the respective therapies administered.

Comparable proportions of patients in the pembrolizumab combination and control experienced AEs (98.2% vs 97.9%), Grade 3-5 AEs (69.8% vs 68.2%) and SAEs ([redacted] % vs [redacted] %). Drug-related AEs ([redacted] % vs [redacted] %), drug-related Grade 3 to 5 AEs ([redacted] % vs [redacted] %) and drug-related SAEs ([redacted] % vs [redacted] %) were observed more frequently with pembrolizumab combination than control, possibly due to the longer duration of exposure in the pembrolizumab combination group.

The most frequently-reported AEs in both treatment groups were among those typically associated with chemotherapy, including anaemia, alopecia, neutropenia and nausea. The majority of AEs were grade 3 or lower and occurred in the first 3 months in the 2 treatment groups, as might be expected given that the chemotherapy components were administered during the first 4 cycles of treatment.

Higher rates of discontinuation of any drug within the treatment regimen due to an AE occurred in the pembrolizumab combination compared with the control (23.4% vs 11.8%), which was primarily driven by a higher rate of discontinuation of pembrolizumab (17.3%) compared with placebo (7.9%). Similar trends were also observed in discontinuations due to drug-related AE, serious AE, and serious drug-related AE. The differences in discontinuation rates between the treatment groups may be attributable to the longer duration of exposure in the pembrolizumab combination. Patients in the control were more likely to discontinue treatment for PD.

The incidence of AEOSIs was higher in the pembrolizumab combination group (28.8%) than the control (8.6%). The most frequent AEOSIs (>5%) in the pembrolizumab combination were hypothyroidism (7.9%), hyperthyroidism (7.2%), and pneumonitis (6.5%). (Table 53)

The incidence of AEOSIs in the pembrolizumab combination group was consistent with that seen in patients with lung cancer treated with pembrolizumab monotherapy; these AEs were not exacerbated by the addition of carboplatin/paclitaxel (or nab-paclitaxel) in the pembrolizumab combination group.

Internal Validity

KEYNOTE-407 is a robust, multicentre, randomised, active-controlled, double-blind phase III trial of pembrolizumab combination versus control in previously untreated adults with metastatic squamous NSCLC. The co-primary efficacy endpoints were OS and PFS; both clinically relevant endpoints that were directly referenced in the final scope for this appraisal and the decision problem. Moreover, the endpoints selected are consistent with those used in studies of other therapeutic agents in the population of metastatic NSCLC. The definition of progression when evaluating the primary endpoint of PFS in KEYNOTE-407 followed an established response evaluation criteria (RECIST 1.1) in the primary efficacy analysis, in line with European guidance.[87]

In addition to being double blind, with both patients and clinicians blinded to treatment assignment, for PFS analysis, the independent radiologists who performed the central imaging review were also blinded to treatment assignment, in order to minimise bias.

HRQoL was an exploratory endpoint of the KEYNOTE-407 study assessed using EQ-5D (the preferred measure according to the NICE reference case) as well as cancer specific EORTC QLQ-C30 and lung cancer specific EORTC QLQ-LC13.

Patient demographics and clinical characteristics were similar across both treatment groups in terms of all subject characteristics assessed including gender, age, ethnicity, geography, smoking status, ECOG performance status, disease stage and PD-L1 expression.

External validity

KEYNOTE-407 was a global study conducted in 137 academic medical centres in 17 countries. Of the patients participating in the study, 42.9% were enrolled at sites in Europe.

Baseline characteristics of patients enrolled in KEYNOTE-407 were as expected for patients with advanced NSCLC. The majority of patients were male, white, with mean age around 65 years old and most were current or former smokers.

The observed safety profile of pembrolizumab combination in KEYNOTE-407 was consistent with that seen previously with pembrolizumab for the treatment of advanced NSCLC [13, 14] and other types of tumours.[88-92]

End-of-life criteria

An overview of published data on life expectancy of UK patients with metastatic squamous NSCLC was provided in Section B.1.3.1. To recap: There is a paucity of data reporting long-term survival of patients with metastatic squamous NSCLC patients in the UK. The most recent data from the National Cancer Registration and Analysis Service – Public Health England (based on diagnoses from 2012 to 2014) indicate one-year survival of 15% for men and 19% for women diagnosed with Stage IV lung cancer.[25]

In recent years, newer treatment options have become available for NSCLC patients with advanced disease, including pembrolizumab monotherapy for patients with high levels of PD-L1 expression (TPS ≥50%) which can be expected to increase the long term survival estimates over first-line SoC patients. However, in the absence of recently published long-term survival expectations for UK patients with metastatic squamous disease, we consulted expert physicians for estimates of survival based on their experience in clinical practice. The physicians reported 5 year survival in metastatic squamous NSCLC patients of between 0 and 8% citing recent advances in care in the 2L setting but also that many patients do not make it to 2L therapy, indicating that the first of the end-of-life criteria should be met and that significant unmet need remains for life-extending treatment options for this patient population.

Based on the clinical data from IA2 analysis of KEYNOTE-407, the median OS for the pembrolizumab combination group was 15.9 months compared with 11.3 months for the control group; a difference of 4.6 months, which is greater than the minimum required 3 month extension to life.

Table 54: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	In KEYNOTE-407 trial, median OS in the pembrolizumab combination arm was 15.9 months compared with 11.3 months in the control arm. The OS of 11.3 months observed in the SoC arm is in line with previous studies where median OS in patients with NSCLC (regardless of histology) receiving chemotherapy SoC ranged from 9.9 to 13.9 months.[15]
There is sufficient evidence to indicate that the treatment	Pembrolizumab combination offers an extension to life of at least 3 months compared to SoC: • The estimated different in median OS, based on the latest analysis of

Criterion	Data available
offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	KEYNOTE-407 data, was 4.6 months in favour of pembrolizumab combination-treated patients vs SoC.[4] • The estimated difference (based on discounted values) from the cost-effectiveness model are: o 27.1 months (ITT base case 48.3-21.2)

B.2.14 Cancer Drugs Fund suitability

Within this submission MSD is seeking a recommendation for pembrolizumab combination for use within the CDF as a treatment for adults with untreated, metastatic, squamous non-small-cell lung cancer (NSCLC).

The rationale for seeking a CDF recommendation is that MSD acknowledges the Committee will believe that more certainty will be required around the OS benefit given the immaturity of the data when it is known that further analyses will be conducted. This is particularly relevant given that the trial, and the MSD base case, cover the entire population irrespective of PDL1 expression.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review was conducted to identify relevant cost-effectiveness studies from published literature and from NICE technology appraisals as per NICE guidance. A single review was carried out on the 3rd August 2018 to identify studies in NSCLC that included published economic evaluations, studies reporting utility values and studies reporting cost and resource use data. While the target population in this submission is patients with squamous histology of NSCLC, the published economic literature often refers to the disease as NSCLC therefore the focus of the search was broadened to NSCLC studies (squamous and non-squamous) so that any relevant evidence that could inform the development and population of the model was not missed. A detailed search strategy is provided in Appendix G. To ensure that important studies are not missed, various sources were searched for evidence: electronic databases, conference abstract books, HTA websites and grey literature among others. A full list of the specific databases is provided in Appendix G.

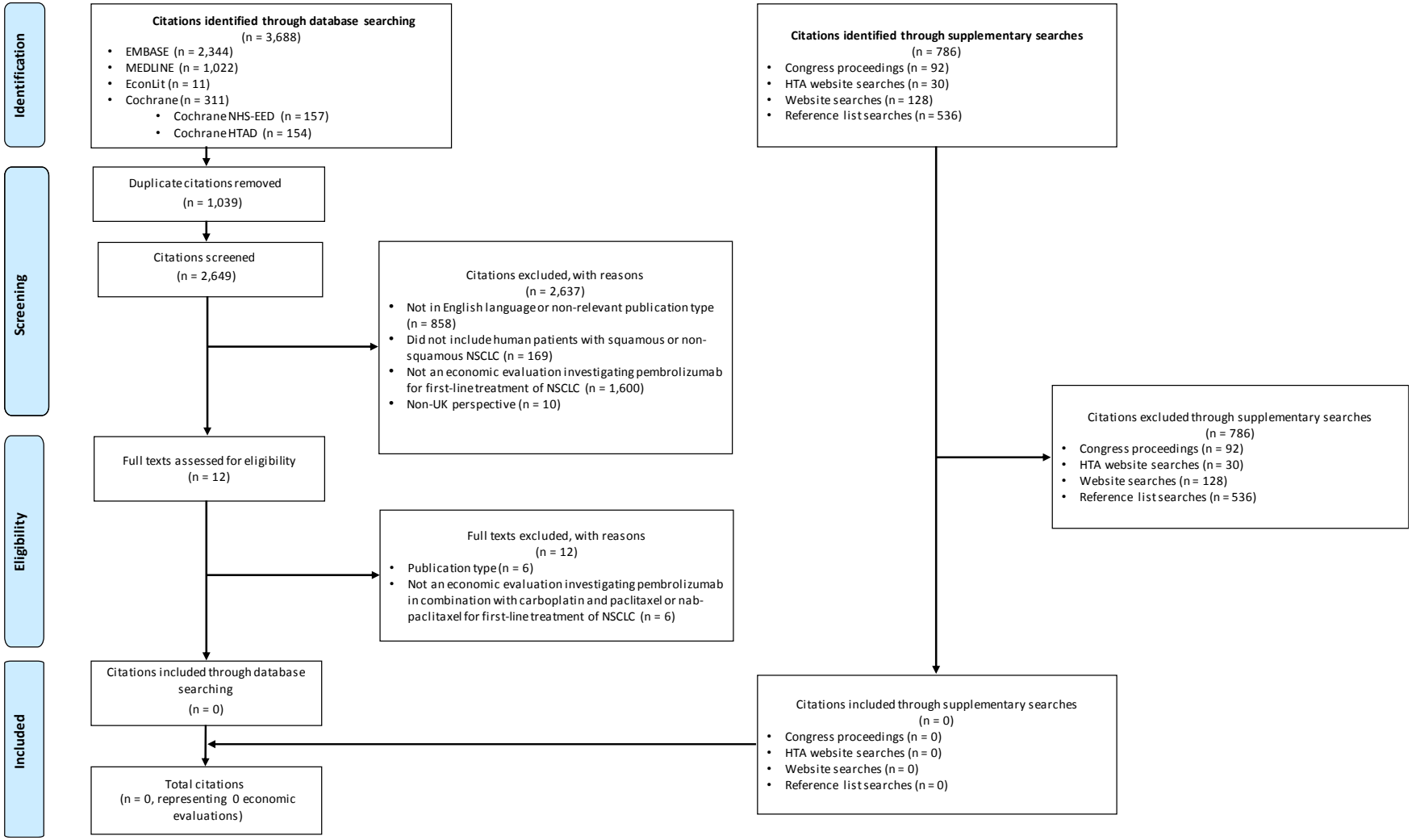
The citations found through the searches were first assessed against the eligibility criteria set out in the final protocol by two independent reviewers based on abstract and title. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. Full-text copies of publications potentially meeting the eligibility criteria were then obtained and reviewed in more detail by the two independent reviewers. The eligibility criteria are presented in Appendix table below

Domain	**Economic evaluations**	
	Inclusion Criteria	**Exclusion Criteria**
Population	Adult (≥18 years) treatment-naïve patients with squamous or non-squamous NSCLC	Individuals without NSCLC, previously treated patients with NSCLC or populations where outcomes are not presented separately for the patients of interest
Intervention(s)	Pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel	Studies not investigating pembrolizumab in the first line, or studies where pembrolizumab

Domain	Economic evaluations	
	Inclusion Criteria	**Exclusion Criteria**
		is not combined with carboplatin and paclitaxel or nab-paclitaxel
Comparator(s)	Any	-
Outcomes	Outcomes of relevant study designs, including: ICERs Cost per clinical outcome Total QALYs Total LYGs Total costs Incremental costs and QALYs	Studies not presenting relevant outcomes for the population of interest
Study design	Any of the following analysis types: Cost-utility Cost-effectiveness Cost-consequence Cost-benefit Cost-minimisation	Any other types of analysis
Publication type	Journal articles presenting original research Systematic reviews of relevant primary publications (these were included at the title/abstract stage and used for the identification of any additional primary studies not identified through the database searches. They were then excluded during the full-text review stage unless they reported primary, original research themselves) HTAs Congress abstracts published in or after 2016	
Other considerations	UK NHS or PSS or Irish HSE or DoH* perspective only English language Human subjects	Non-UK NHS or PSS or HSE perspective Non-English language articles Articles not on human subjects

The database, internet and hand searches identified a total of 4,474 potentially relevant records of economic evaluation, HRQoL and cost and resource use studies. In terms of the economic evaluation studies, 12 of them met the inclusion criteria for full text assessment but no publication presenting economic evaluations of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel was identified; thus a summary of published cost-effectiveness studies was not compiled. These 12 excluded studies are available in Appendix G. The PRISMA flow diagram is presented in Figure 25.

Figure 25.PRISMA flow diagram for the economic evaluations



B.3.2 Economic analysis

Since no cost-effectiveness studies were identified in the target population and intervention, a de novo cost-effectiveness model was developed using the PSM approach as previously used to assess the cost-effectiveness of pembrolizumab in NSCLC [27]. [93] [94]

B.3.2.1 Patient population

The patient population included in the economic evaluation consisted of patients with advanced squamous NSCLC, who received no prior systemic chemotherapy treatment. This is in line with the proposed licenced indication and with the final NICE scope [1].

The main body of clinical evidence for pembrolizumab combination compared to SoC was derived from the KEYNOTE-407 study, which included previously untreated advanced squamous NSCLC patients [4].

The baseline characteristics of the patients included in the model are presented in Table 55.

Table 55. Baseline characteristics of patients included in the model

Patient Characteristics	Mean	Measurement of uncertainty and distribution	Reference / Source
Average age*	65	60-70	KEYNOTE-407
Average BSA (m^2)*	1.86	1.83-1.89	KEYNOTE-407

*These values refer to patients recruited from European sites participating in KEYNOTE-407.

B.3.2.2 Model structure

Consistent with the majority of economic models developed for recent NICE oncology submissions in advanced NSCLC [95, 96] [97] [93], a de-novo economic analysis was built as a 'partitioned-survival' area-under-the-curve model. The model consisted of three mutually exclusive health states below (see Figure 26). Once that distribution is available for each weekly cycle in the model, the proportion of patients that are within various intervals of time until death is calculated (with the use of time to death utility in the base case analysis). This is somewhat similar to applying an age-specific cost to a cohort of patients entering a model at a given age, or an age-specific utility, except that here time is reflected not by age, but by time until death.

- Progression-free state (PF) is the starting health state and defined as the time from the start of the regimen use to disease progression or death (whichever comes first),

- Progressive-disease state (PD), which encompasses time after the first progression, or
- Death.

In this model, progression is defined by blinded independent central review (BICR) using Response Evaluation in Solid Tumors (RECIST) V1.1 criteria [36].

Patients in each cohort start in the "PF" state. At the end of each cycle, patients who are "PF" may stay in "PF", transition to the "PD" state, or die. Patients in the "PD" state may stay in "PD" or die at the end of each cycle. Patients in the "PD" state cannot go back to the "PF" state.

The analyses adopt a partitioned-survival model approach, which partitions overall survival (OS) time into progression-free survival (PFS) and post-progression survival. It is very similar to a Markov model, where outcomes (costs, life years, and quality-adjusted life years) are evaluated for each health state.

However, unlike in a Markov model, in which transition probabilities between any two health states are needed, a partitioned-survival model directly estimates the proportions of patients in each health state at each time point. Using the partitioned-survival approach has the advantage of being able to utilise the trial PFS and overall OS data directly, without separate estimation of transition probabilities. PFS and OS are common primary and/or secondary endpoints in pivotal advanced cancer randomized clinical trials.

Below is how the proportion of patients in each health state is calculated at a certain time point:

- PF: proportion of patients with PFS, as calculated from the PFS curve
- Death: 1- (proportion of patients who are alive, as calculated from the OS curve)
- PD: (proportion of patients who are alive, as calculated from the OS curve) – (proportion of patients with PFS)

For each health state, a specific cost and quality-of-life adjustment weight (i.e. utility) is assigned within each time period for calculating the cumulative costs and cumulative quality-adjusted life years over a course of time.

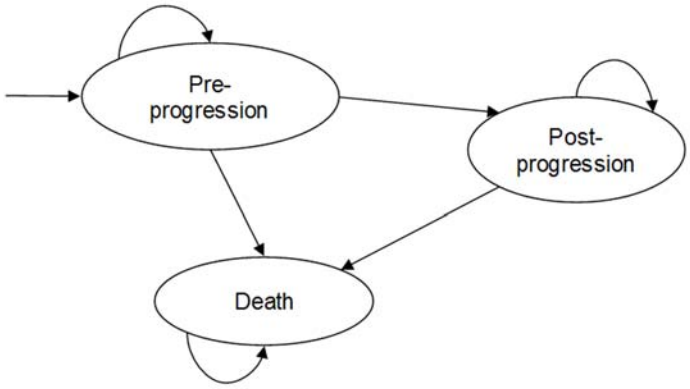
The definition of the health states used in the model was based on the definitions conventionally used in oncology clinical trials and, specifically, the ones used in the pembrolizumab combination KEYNOTE-407 trial:

- Progressive disease was defined following the RECIST 1.1 criteria, i.e., at least a 20% increase in the sum of diameters of target lesions, and an absolute increase of at least 5 mm, or appearance of one or more new lesions [98, 99].
- Non-progressive disease reflected patients being alive and not in progressive disease (which included patients with complete response, partial response and stable disease).
- Death (absorbing health state).

This approach was also in line with the clinical endpoints assessed in KEYNOTE-407, in which PFS and OS were assessed as primary endpoints [36] and is consistent with previous economic modelling in NSCLC [94, 100 101 102 103-105 93].

A cycle length of one week was considered sufficient to reflect the patterns of treatment administration and the transitions to disease progression and death. In line with previous submissions, a half-cycle correction was applied to mitigate bias [103 101 106 96 94, 100 97 104, 105 93].

Figure 26. Model structure



For the base case, and in line with the analyses conducted for KEYNOTE-407, two treatment arms were compared, pembrolizumab combination (pembrolizumab plus paclitaxel or nab paclitaxel and carboplatin (pembrolizumab combination) and SoC (placebo plus paclitaxel or nab paclitaxel and carboplatin).

In the model, patients in the pembrolizumab combination arm were assumed to be eligible to receive treatment until progression or for a maximum treatment duration of 2 years

(consistent with the 35 cycle maximum for trial protocol) with pembrolizumab and 4 cycles with chemotherapy consistent with the KEYNOTE-407 trial protocol [36]. Additionally, the current NICE recommendations for the use of pembrolizumab monotherapy for the treatment of advanced NSCLC states that pembrolizumab is to be stopped at 2 years of uninterrupted treatment [94, 100].

Patients treated with SoC were also assumed to receive treatment until a maximum number of 4 cycles, aimed to reflect clinical practice in England (see section B.3.5).

Since patients in KEYNOTE-407 could receive subsequent oncologic therapies after treatment discontinuation, the costs of these subsequent treatments were included in the economic evaluation according to the proportion of patients receiving them after treatment discontinuation from the trial. In addition, cross over from the SoC arm to pembrolizumab was allowed during the trial but since 2L IO therapy is standard of care in the UK for patients with squamous NSCLC [94] [27] [107], cross over adjustment has not been implemented in the ITT base case analysis.

Subgroup analysis at different levels of PD-L1 expression (≥50%, 1%≤TPS≤49% and <1% TPS) has been conducted.

To capture more accurately the impact of pembrolizumab combination upon quality of life, the utilities considered in the base case analysis were based on time-to-death categories. Time-to-death sub-health states were used to capture patients' quality of life as a function of how much lifetime patients had left until they eventually died as predicted in the model. The use of time-to-death sub-health states was applied considering four time-to-death categories: <30 days to death and ≥30 days to 180; ≥180 to 360 days, and ≥360 days. Monitoring costs were captured based on whether patients were receiving active therapy as part of first or second treatment lines, and also based on their progression status [108].

3.2.3 Key features of the economic analysis

Table 56: Features of the economic analysis

		Current appraisal	
Factor	**Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (2017) NICE technology appraisal 531**	**Chosen values**	**Justification**
Time horizon	Lifetime (30 years)	Lifetime (30 years)	Lifetime horizon for the defined target population (2% of patients in the pembrolizumab combination arm and 0% in the SoC arm were still alive after this period in the base case).
Cycle length	1 week	1 week	Sufficient to model the patterns of treatment administration, transitions to disease progression and OS. In line with a recent NICE submission in advanced NSCLC[94, 100].
Half-cycle correction	Yes	Yes	In line with previous submissions and to mitigate bias[94, 100, 109]
Were health effects measured in QALYs; if not, what was used?	Yes	Yes[110]	NICE reference case Please note that direct health effects related to patients were considered, but the impact on carers has not due to the unavailability of data to incorporate this into the model
Discount of 3.5% for utilities and costs	Yes	Yes[110]	NICE reference case
Perspective (NHS/PSS)	NHS	Yes[110]	NICE reference case. Please note that the costs to the NHS were included, but PSS costs have not been considered due to the unavailability of data to incorporate this into the model. This is also in line with previous NICE submissions for first line therapies[94, 100, 109].
Treatment waning effect	Considered in scenario analyses	Considered in scenario analysis.	There is no evidence that treatment effect stops after discontinuation. Considered in scenario analyses

		Current appraisal	
Factor	**Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (2017) NICE technology appraisal 531**	**Chosen values**	**Justification**
Source of costs	Published literature, resource utilisation and costs accepted in previous NICE submissions	Published literature, resource utilisation and costs accepted in previous NICE submissions	These reflect resource utilisation and costs accepted in previous NICE submissions.

B.3.2.3 Intervention technology and comparators

The intervention (pembrolizumab combination) was included in the model as per the proposed licensed dosing regimen (i.e.pembrolizumab administered intravenously at a fixed dose of 200 mg over 30 minutes combined with carboplatin AUC 6 plus paclitaxel (200mg/m2)/nab-paclitaxel (100mg/m2) 3QW for 4 cycles followed by pembrolizumab 200mg 3QW until disease progression.

The proposed licence states that pembrolizumab is to be administered until disease progression or unacceptable toxicities. There is no evidence regarding the optimal duration of treatment with pembrolizumab; however, the KEYNOTE-407 protocol mandated a maximum of 35 cycles of pembrolizumab (2 years).

In line with the comparator assessed in KEYNOTE-407, SoC (based on the trial chemotherapy arm) was considered as the comparator of relevance in the cost-effectiveness model. It is noted that the comparator arm in KEYNOTE-407 has only a small market share in UK clinical practice (2%). Since there is a lack of published data in this patient population, and based on evidence detailed in section B.2.8 it was assumed that the comparator arm in KEYNOTE-407 is equivalent to other platinum chemotherapy options available in the UK with which clinical experts have agreed [107] [95].

- In the base case, distribution of paclitaxel and nab paclitaxel observed in KEYNOTE-407 was used to be consistent with the efficacy inputs of the model. In addition, there is evidence to suggest that paclitaxel and nab-paclitaxel are not significantly different in terms of OS [39]. The use of UK specific market of the distribution of carboplatin vs. cisplatin use within platinum chemotherapy regimens in stage IV squamous NSCLC of SoC chemotherapies in this patient population was tested in a scenario analysis.

- Due to its inclusion in the NICE scope [1], an ITC was conducted in order to make a comparison against pembrolizumab monotherapy (≥50%TPS only). Please note, the results of the ITC are not statistically significant. Further detail available in B.2.8 and B.2.9.

The following comparators were also included in the NICE scope [1] for which a network meta-analysis was conducted. Due to a paucity of data in the target patient population, a comparison versus vinorelbine plus platinum was not available. Further detail available in B.2.8 and B.2.9.

- Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin).

Table 57. Distribution of patients according to platinum-based chemotherapy combinations in KEYNOTE-407 vs. market shares

	KEYNOTE-407 (base case)	UK market shares distribution of carboplatin vs. cisplatin use within platinum chemotherapy regimens in stage IV squamous NSCLC[111]
Gemcitabine/carboplatin	n/a	69%
Gemcitabine/cisplatin	n/a	31%
Nab-Paclitaxel/carboplatin	39.9%	0%
Nab-Paclitaxel/cisplatin	n/a	0%
Paclitaxel/carboplatin	60.1%	93%
Paclitaxel/cisplatin	n/a	7%
Docetaxel/carboplatin	n/a	63%
Docetaxel/cisplatin	n/a	37%
% Total	100%	100%

The dosing and administration frequencies for these comparators were applied in the model in line with their marketing authorisations and UK clinical practice.

The type of comparisons assessed in the cost-effectiveness model is presented in Table 58.

Table 58. Intervention and comparators according to the different types of analyses assessed in de novo cost-effectiveness model

Population	Intervention and comparators	Clinical evidence derived from:	OS for comparator arm			
	Pembrolizumab vs.		unadjusted	Two-stage	RPSFT	IPCW
ITT population	▪ Carboplatin + Paclitaxel/nab-paclitaxel	KEYNOTE-407	✓	×	×	×
Subgroups						
≥50% TPS	▪ Carboplatin + Paclitaxel/nab-paclitaxel ▪ Pembrolizumab mono	KEYNOTE-407 ITC	✓	×	×	×
1%≤TPS≤49%	▪ Carboplatin + Paclitaxel/nab-paclitaxel	KEYNOTE-407	✓	×	×	×
<1% TPS	▪ Carboplatin + Paclitaxel/nab-paclitaxel	KEYNOTE-407	✓	×	×	×

ITT = intention to treat

B.3.3 Clinical parameters and variables

B.3.3.1 Overall method of modelling OS and PFS

The primary data source for the economic model was the data derived from the KEYNOTE-407 clinical trial. Data from the April 2018 data cut has been used for the clinical parameters of the cost-effectiveness model, including OS, PFS and safety.

Survival modelling – OS (base case) SEER Data

As an initial modelling approach, parametric models were fitted to KM full OS dataset to extrapolate outcomes over the model time horizon. In brief, with The KM data used for 19 weeks and the parametric model fitting used KM data from after 19 weeks until the end of available trial follow-up. Further details available in Appendix L.The survival curve fitting was carried out in line with NICE Decision Support Unit (DSU) guidelines [112]. The parametric models fitted reflected Weibull, exponential, lognormal, log-logistic, Gompertz and generalized gamma distributions. Statistical tests based on the Akaike Information Criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to select the best-fitting parametric distributions for the base-case. Finally, the clinical plausibility of the extrapolated results was considered in selecting the final distribution functions for the model, such as rejecting distributions with an implausibly flat long-term survival curve based on published evidence or clinical opinion or leading to a non-justifiable crossing of survival curves.

It was found that standard statistical-based fitting utilising data from within the period of the trial provides potentially clinically implausible OS results for the SoC arm of 1-2% at 5 years. It is thought that this is unrealistic given the advances in care in this patient population and the introduction of 2L IO therapy. In a recent NICE TA in this patient population in second line [107], the committee agreed that the LYG for 2L patients who would receive the assessed treatment would be 16.01 months. It can be assumed then that in addition to 4 cycles of 1L platinum chemotherapy available as the 1L SoC for these patients would bring this to around 19 months. Although, equivalence between the KEYNOTE-407 and clinical trial utilised in the aforementioned TA (Checkmate-017) cannot be inferred, the patient characteristics and potential outcomes can be considered broadly similar for at least the 52% of the KEYNOTE-407 population who go on to receive a 2L therapy following SoC in the economic model.

Although not in the same patient population, but with inclusion of squamous histology patients in the clinical trial, during TA447 and its review (TA531) [27], the ERG preferred a time cut which produced an estimate of 9.6% survival at 5 years and 1.5% at 10 years due to the availability of IO drugs in 2L SoC for the PD-L1 positive patients even suggesting 5 year estimates could be as high as around 17%. The ERG also mentioned the CRUK data of 10% alive at 5 years and 5% at 10 years. However OS at stage 4 is not available as there are such a small number of people surviving more than 2 years [113].

To this end it was considered necessary to assess longer term OS for the trial chemotherapy arm using available population data for squamous NSCLC patients and compare to results from parametric fitting. This was unfortunately not available in a UK population but available for a US cohort from the U.S. Surveillance Epidemiology and End Results (SEER) program. Data from 1992-2014 were analysed for metastatic squamous NSCLC patients [114] . As patients within the KEYNOTE-407 trial were an average of 2 months from their date of diagnosis with metastatic squamous NSCLC at baseline, survival within the SEER database was similarly analysed starting from 2 months post-diagnosis. SEER data from 2010-2014 were utilised to assess survival during years 1-5 of follow-up, data from 2000-2014 for years 6-10 of follow-up and data from 1992-2014 for years 11-13 of follow-up. Beyond 13 years, there was insufficient sample size within SEER for stable reporting of estimates.

Within the SoC arm in KEYNOTE-407, 46 patients had KM survival data available for at least 12 months, with very few patients with data available, and no death events, occurring beyond 15 months. In order to demonstrate the potential overestimation of the parametric modelling approach with real world registry data from SEER, it was therefore elected to compare OS beyond the 12 month time frame in which trial KM could be potentially be utilised for the SoC arm between that projected by the parametric fitting approach (described in appendix L) and SEER population data (Table 59).

Table 59: SoC Arm OS During Model Years 2-13 Based on Parametric Statistical Fitting vs. SEER Population Data for SQ NSCLC

	Annual Mortality Risk		% of Patients Alive at Start of Year	
Year	Parametric Extrapolation	SEER	Parametric Extrapolation	SEER
2	58.1%	54.3%	48.5%	48.3%
3	58.1%	41.2%	20.3%	22.1%
4	58.1%	22.5%	8.5%	13.0%

5	58.1%	21.9%	3.6%	10.1%
6	58.1%	19.7%	1.5%	7.9%
7	58.1%	16.4%	0.6%	6.3%
8	58.1%	16.0%	0.3%	5.3%
9	58.1%	12.9%	0.1%	4.4%
10	58.1%	11.9%	0.0%	3.9%
11	58.1%	16.9%	0.0%	3.4%
12	58.1%	8.0%	0.0%	2.8%
13	58.1%	9.9%	0.0%	2.6%

As shown in the table, the modelled exponential (best statistical and visual fitting) distribution parametric fitting approach projects a constant 58.1% mortality risk over time, which is similar to the mortality risk observed within SEER in year 2 (54.3%), but consistently higher than SEER-observed risks in subsequent years. Mortality risks within SEER progressively decline until around year 10 and then appear to stabilize in the range of roughly a 10% risk per year. This is consistent with a greater number of the subset of surviving patients attaining disease remission or cure in the longer run. Because the parametric extrapolation carries forward mortality experiences observed during the latter portion of the available clinical trial data (based on mortality observed during the latter portion of year 1 and start of year 2), when patients are experiencing a high risk of mortality, use of the best fitting parametric extrapolation is very likely to over-estimate long term mortality based on data from after week 19, to the last available follow-up time point, which is around week 80.

The degree of over-estimation could even be conservatively estimated here as the trial population might otherwise be expected to have a lower risk of mortality relative to the SEER population, due to exclusion of patients with certain co-morbidities or who were anticipated to be very close to death, and the availability of advances in 2L+ treatments not available for all or a portion of the period of the SEER time horizon. Nonetheless, a comparison of trial SoC arm mortality risks during months 7-12 of the KEYNOTE-407 trial (data are insufficient for a month 13-18 analysis) suggests a fairly similar risk (37%) to that observed over an analogous time horizon in SEER (43%).

An additional analysis of an alternative US database (Flatiron) was also conducted using the same criteria as the SEER database analysis [115] . Flatiron is a US database utilising over 2M active patient records across 280+ community oncology practices [116] . This was to attempt to validate further the use of SEER within the modelling framework since Flatiron has more recent data however not enough granularity to use in the CE model. Table 60 shows the

year 1 and 2 risk of mortality from year of diagnosis 2011-16. It can be seen that the 2 year risk of mortality from the furthest back time point of 2011 is 55.9% which is very similar to that reported in the SEER analysis at year 2 of 54.3%. This suggests not only confidence in the proposed risk of mortality applied in the CE model but also that this estimate could be considered conservative with more recently diagnosed patients in Flatiron having much reduced 2 year mortality estimates of around 45%. In addition, the Flatiron data can provide an insight into the impact of the introduction of 2L IO therapy availability since its introduction in the US in 2015 which post-dates the SEER data analysis. It can be seen that in general the risk in mortality is declining over time as new advances of care are introduced again suggesting that the SEER data analysis used in the model could in fact be conservative for SoC today in the UK and going forwards since the first 2L IO in this population was approved by NICE in November 2017 [107].

Table 60 FlatIron database Annual risk of mortality rate from 2011-2016

Year of advanced diagnosis	Year 1[a] risk of mortality	Year 2[b] risk of mortality
2011	71%	55.9%
2012	64.8%	54%
2013	62.6%	46%
2014	63%	42.8%
2015	57.1%	45.2%
2016	61.3%	NA[c]

a. 3 – 14 months
b. 15 – 27 months
c. Data maturity hasn't reached at 27 months; number of patients in risk at month 27 is less than 10% of cohort size

Thus, for base case modelling purposes within this report, it is elected to utilise the KEYNOTE-407 KM data for the SoC arm for model months 1-12 and SEER-based annual mortality risks thereafter, with a constant 9.9% annual mortality risk as observed in year 13, extrapolated for model years 14+. These risks are applied for the ITT population as well as each PD-L1 sub-group.

For the pembrolizumab combination arm, Table 61 reports mortality risks during months 1-6 and 7-12 of the KEYNOTE-407 trial, as compared to the SoC arm and the corresponding relative risk. The relative risk for the latest available 6-month time window (0.58), is applied to the SEER-based SoC arm mortality risks in Table 59 to estimate annual mortality risks for pembrolizumab combination during model years 2-5 (Table 62). Within PD-L1 sub-groups, HRs reported over the full trial time period are nearly identical for the PD-L1 ≥ 50% (0.64, 0.37-1.10), PD-L1 1-49% (0.57, 0.36-0.90) and PD-L1 <1% (0.61, 0.38-0.98) sub-groups [4]. However, when evaluating relative risks for months 7-12 within each sub-group, there was

found to be a wide degree of variability, with values of 0.79, 0.64 and 0.45 estimated for the PD-L1 ≥ 50%, PD-L1 1-49% and PD-L1 <1% sub-groups respectively, likely due to sparse data within each month 7-12 window. As it did not seem clinically plausible for there to be a substantially higher efficacy in PD-L1 < 1% patients as compared to PD-L1 ≥ 50% patients, and given the high degree of similarity in HRs across sub-groups using data from the full trial period, it is elected to instead apply the relative risk for the overall population (0.58) within each modelled sub-group, in estimating mortality risk reductions during years 2-5.

Table 61: 6-month Mortality Risks, and Relative Risks, for Pembrolizumab combination in KEYNOTE-407

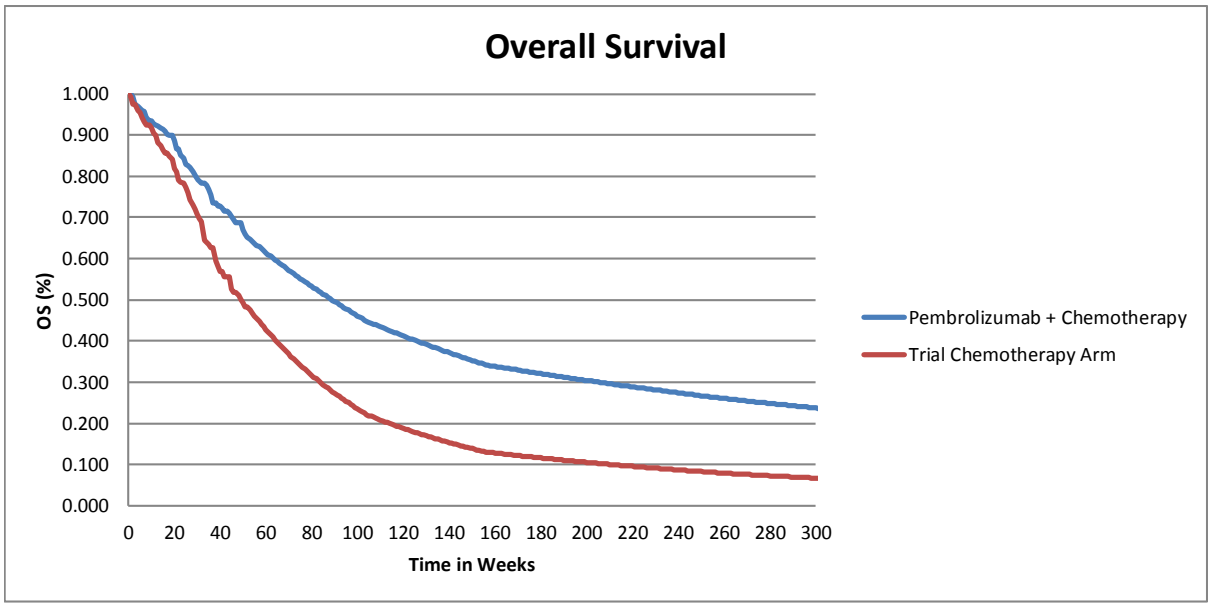
	6-month Mortality Risk		Pembrolizumab combination vs. SoC	
Month	Pembrolizumab combination	SoC	Relative Risk	95% Confidence Interval
1-6	17.4%	23.9%	0.73	0.51 - 1.02
7-12	21.1%	36.5%	0.58	0.38 - 0.87

Table 62: Annual Mortality Risks During Model Years 2-5 By Treatment Arm

	Annual Mortality Risk	
Year	Pembrolizumab combination	SoC
2	31.3%	54.3%
3	23.7%	41.2%
4	13.0%	22.5%
5	12.6%	21.9%

Figure 27 displays OS curves by treatment arm within the overall trial population during years 1-5, where data for year 1 reflect trial KM data and for years 2-5 the SEER population-based extrapolation approach just described.

Figure 27: OS By Treatment Arm, Years 1-5

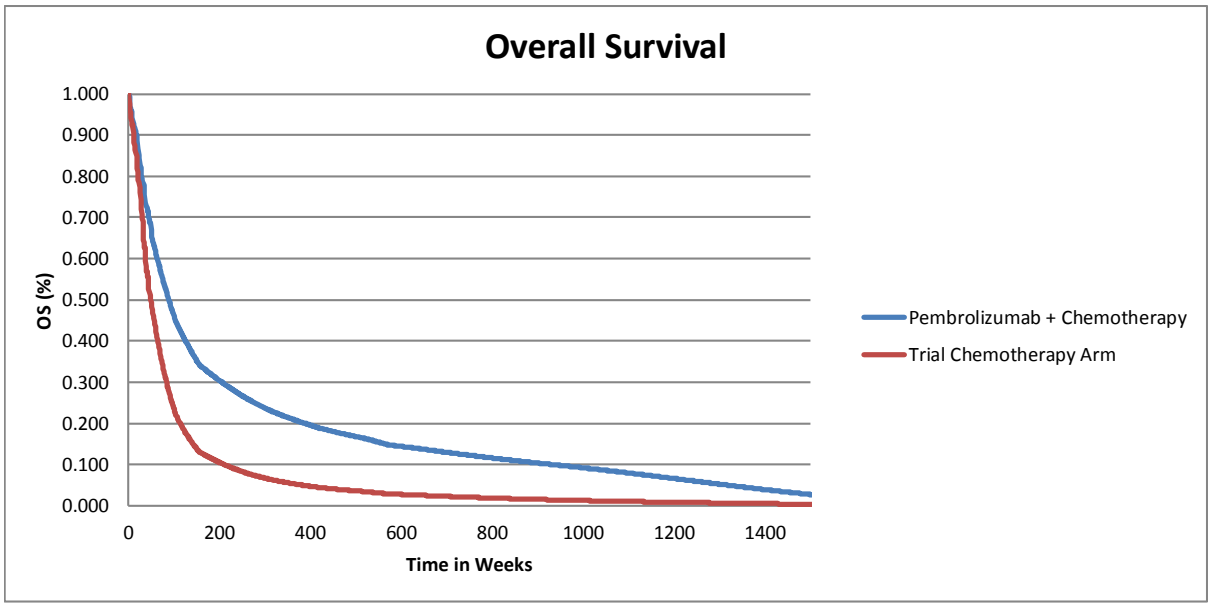


In scenario analysis, treatment waning is investigated where beyond model year 5, an identical SEER-based mortality risk, as reported in Table 59, was applied in estimating OS for both the pembrolizumab combination and SoC arms, assuming the long-term survival trend is independent of treatment received. Metastatic NSCLC patients initially randomized to 2nd line treatment with Pembrolizumab monotherapy vs. docetaxel chemotherapy in KEYNOTE-010 have been observed to have a sustained clinical overall survival benefit out to at least 3 years [117] (Merck data on file), and a 5 year time point for an assumed continued therapeutic benefit for 1L combination therapy benefit would thus seem plausible.

The resulting OS curves over the full 30 year base case time horizon are presented in

Figure 28 for each treatment group.

Figure 28: OS By Treatment Arm, Years 1-30



Comparison of SEER with UK data

The economic analysis utilises SEER US registry data for the long-term extrapolation of overall survival as discussed above. In the UK, the National Lung Cancer Audit (NLCA) looks at the care delivered for people diagnosed with lung cancer and mesothelioma in England, Wales and Scotland, and therefore, survival estimates reported in NLCA can be considered representative of UK clinical practice however published estimates are only available for one year survival in the all histologies NSCLC population [18]. MSD have contacted the NLCA in order to obtain further longer term UK data if available and have so far been unable to do so. SEER is a co-ordinated system of population based cancer registries located across the US; data are collected on cancer incidence and survival from 18 geographic areas comprising nearly 30% of the US population, and the population covered by SEER is comparable to the general US population [118] .

Given that NLCA data were only available for up to 1 year, SEER registry data were an important source for extrapolation of the long-term survival projections. The comparability of US and UK cancer statistics were assessed by undertaking a comparison of key epidemiological and mortality trends, as reported in Table 63 and Table 64. The UK NLCA data is reported from time of diagnosis. Within the KEYNOTE-407 mortality risk adjustment using SEER utilised in this economic evaluation, data were taken from SEER post 2 months from diagnosis to be in line with the KEYNOTE-407 trial protocol [36] . In Table 63 below,

SEER data has been adjusted to time from diagnosis to provide a more like for like comparison with the NLCA estimates. This assessment revealed that, in general, epidemiological and survival statistics are consistent across the UK and US for lung cancer. Specifically, for incidence, deaths, mortality, and proportion alive by year, as well as the stage distributions at diagnosis and trends in age at diagnosis are consistent across populations in the UK and the US. Additionally, baseline characteristics of patients registered in the KEYNOTE-407 trial were compared with those of patients in the SEER and NLCA registries, and this comparison is presented in Table 65. A limitation in the comparison is the lack of data describing patients by line of therapy, type of therapy and performance status, however, the overall conclusion is that the baseline demographics of UK and US registries are not dissimilar to each other and the trial patients providing further justification for the long-term extrapolations based on these RWD.

Table 63: Comparison of UK and US data for lung cancer

	UK	US
Incidence	71.2 per 100,000 (2015) [119]	54.6 per 100,000 (2015) [120]
Estimated new cases	13% of all cancers [119]	13.5% of all cancers[120, 121]
Estimated Deaths	19,314 (2016) – 21% of all cancer deaths[24]	154,050 (2018) – 25% of all cancer deaths
Mortality	54.3 per 100,000	43.4 per 100,000
Proportion alive 1 year (stage IV)	15.5%[18]	23.8%
Proportion alive 5 years (stage IV)	Not available	3.0% [120]

Table 64: Comparison of stage distribution for lung cancer across the UK and US

Stage %	I	II	III	IV	Unknown
UK[119]	15%	7%	19%	48%	10%
US[120]	16%		22%	57%	5%

Table 65: Comparison of baseline characteristics from KEYNOTE-407, SEER and NCLA

	KEYNOTE-407 [4]	SEER [122]	NCLA [18]
Median age	75	70	72[123]
% Male	36.4%	65% (2010-14)	58%[123]

Survival modelling – parametric approach PFS and OS (scenario analysis)

To extrapolate the PFS and OS (in scenario analysis) from KEYNOTE-407, to populate the area-under-the-curve (AUC) partitioned survival approach, guidance from the NICE DSU

was followed to identify base case parametric survival models for OS and PFS [112]. In summary, the steps that were followed include:

- Testing the proportional hazard (PH) assumption – To assess whether joint or separate statistical models were more appropriate for the pembrolizumab combination and SoC treatment arms:
    - A statistical test of the PH assumption was performed
    - The cumulative hazard plot, the log cumulative hazard plot and the Schoenfeld residual plot were visually assessed to determine if the data from KEYNOTE-407 indicated proportional effects between pembrolizumab combination and SoC.
- A comprehensive range of pooled parametric survival models were explored. Data from both treatment arms were used within the same model, considering and comparing all the relevant standard parametric models (i.e. exponential, Weibull, Gompertz, log-logistic, log-normal and generalized gamma). Since there was evidence against the PH assumption, a pooled parametric model was deemed inappropriate.
- Independent separate survival models were then explored. Models 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.
- 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.
- Lastly, the choice of base case parametric models was validated in terms of clinical plausibility of both short-term and long-term extrapolations.

OS (in scenario analysis) and PFS for pembrolizumab combination and SoC were modelled using a piecewise approach:

- For details of the OS scenario analysis please refer to Appendix L. KEYNOTE-407 KM data was used for the first 19 weeks, on the basis of the changes to cumulative hazards, and two different models were applied following standard parametric approaches:
    - Exponential model – as the statistically and visually best fitting
    - Log Logistic – as the model which predicted OS at 5 years most in line with real world US SEER registry data (11% vs 7.9%).
- For PFS, KEYNOTE-407 KM data was used during the first 26 weeks, to reflect the protocol driven fall in PFS observed alongside the initial radiologic assessments. This was followed by extrapolating using a Log normal model. Other functional forms and two additional cut-offs were assessed in sensitivity analyses (i.e. week 16 and week 36).

Further details of the steps followed to select the relevant methods and data cuts for the OS scenario analysis and PFS are presented in Appendix L, 'Modelling overall survival'.

B.3.3.2 Adverse events

The AEs considered in the model include Grade 3+ AEs which occurred in at least 5% of patients (at any grade) in either treatment arm.

The approach to identify the relevant AEs to be included in the economic model was validated by clinical experts and has been previously accepted in other 1L NSCLC submissions [94, 100].

The incidence of AEs was taken from the KEYNOTE-407 trial for each treatment arm (see

Table 66). It should be noted that the incidence rates of Grade 3+ AEs included in the model can be lower than the 5% cut-off used for inclusion since this 5% cut-off is based on AEs of any grade. The unit cost and the disutility associated with the individual AEs were assumed to be the same for AEs occurring across treatment arms, and the difference in terms of AE costs and disutilities were driven by the AE rates presented in

Table 66. This was consistent with the methods used in previous submissions [124,93] and ensures the full cost and HRQoL impact associated with AEs are captured for both treatment arms without discounting.

In the base case, the impact of AEs was incorporated by estimating weighted average costs per patient, applied as a one-off cost. These were then applied in the first cycle of the model for each treatment arm. AE-related disutilities were considered as part of the base case since this was the preferred approach by the committee assessing the submission for pembrolizumab for the treatment of patients with advanced NSCLC and PD-L1 positive tumours who have been previously treated [94, 109].

Table 66. Grade 3+ AE rates for AEs included in the economic model based on KEYNOTE-407 data[40]

Adverse Event	Risk for pembrolizumab combination	Risk for SoC
Nausea	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea (grade 2)	[redacted]	[redacted]
Diarrhoea (grade 3-4)	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Neuropathy Peripheral	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Peripheral Sensory Neuropathy	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]

Haemoptysis	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Pruritis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Neutrophil Count Decreased	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Platelet Count Decreased	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Hypocalcemia	[redacted]	[redacted]

B.3.3.3 Inputs from clinical experts

We were able to arrange meetings with clinical oncologists working in lung cancer to discuss key issues. We validated the plausibility of the approach to modelling OS using SEER data as a validation to which it was deemed robust.

B.3.4 Measurement and valuation of health effects

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

HRQoL was evaluated in the KEYNOTE-407 trial using the EuroQoL EQ-5D-3L. HRQoL analyses conducted from the trial data were utilitsed for the purpose of the economic section and the estimated utilities were used in the cost-effectiveness model. Evaluation of HRQoL using EQ-5D directly from patients is consistent with the NICE reference case [110].

In the KN407 trial, the EQ-5D questionnaire was administered at each of the first 7 treatment cycles, then every 3rd cycle (9 weeks), for up to 48 weeks while on treatment. The EQ-5D was also administered at a treatment discontinuation visit and at the 30-day post treatment

safety follow-up visit. The EQ-5D analyses presented below are based on the FAS population for the pembrolizumab combination and the SoC arms, to be consistent with the licenced indication and the treatment arms included for the estimation of PFS, OS and safety from KEYNOTE-407 included in the economic model (cut-off date: April 2018).

When estimating utilities, two approaches were considered:

- Estimation of utilities based on time-to-death

  This approach reflects the known decline in cancer patients' quality of life during the terminal phase of the disease. The approach has been previously used in the estimation of HRQoL in patients with advanced NSCLC who had previously received platinum based chemotherapy or palliative radiotherapy [125] [94, 126] and in advanced melanoma patients [127{Batty, 2012 #14}128]. Time to death has been demonstrated as more relevant than progression-based utilities since by considering more health states it offers a better HRQoL data fit [127{Batty, 2012 #14}128].

  Based on KEYNOTE-407 EQ-5D data, time to death was categorized into the following groups:

  - 360 or more days to death
  - 180 to 360 days to death
  - 30 to 180 days to death
  - Under 30 days to death.

  EQ-5D scores collected within each time category was used to estimate mean utility associated with that category. The analyses of the intervals related to time to death lower than 360 days focused on patients with observed death dates. The justification to exclude patients whose death dates were censored was that their EQ-5D values could not be linked to their time-to-death category. However, for the category of 360 or more days to death, patients with censored death date of 360 days or longer were also included since their EQ-5D data related to a survival of at least 360 days, independent of when the death date was censored.

- Estimation of utilities based upon whether or not patients have progressive disease.

  Another approach, more commonly seen in previous oncology economic modelling literature, is to define health states based on time relative to disease progression. While this approach generates results to fit the economic model by health state, there

is a practical issue with the KEYNOTE-407 trial-based utility, where the utility data was collected up to drug discontinuation or at the 30-day-post-study safety follow-up visit, but no further. Therefore, the utility data for post-progression is very limited as it is usually collected right after progression, thus missing the utility data as patients' HRQoL deteriorates when getting closer to death. This leads to an overestimation of the utility in the post-progression state.

Following this approach, the date of progression was determined from the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) using blinded independent central review (BICR).

- To estimate utilities for the progression-free health state, EQ-5D scores collected at all visits before the progression date were used.
- Utilities for the progressive state were based on the EQ-5D scores collected at all visits after the progression date.

For each of the utility approaches, mean EQ-5D utility scores by health status were estimated per treatment arm (pembrolizumab combination and SoC arms), and pooled for both arms. In addition, 95% confidence intervals were obtained for each estimated EQ-5D utility and the statistical significance of the differences between treatment arms was tested.

An analysis conducted to compare baseline EQ-5D utility scores, collected at the first visit (treatment cycle 1), showed that baseline utilities across the two treatment arms were similar.

The above described utility measures were also modelled for pembrolizumab monotherapy. Utility values could differ for pembrolizumab monotherapy, as the absence of a chemotherapy regimen and associated quality of life impacts could favourably impact utilities. Therefore, EQ-5D utility data were utilised from the KEYNOTE-024 trial of pembrolizumab monotherapy versus chemotherapy in metastatic NSCLC. Because patient characteristics may differ between patients in KEYNOTE-024 and KEYNOTE-407, rather than incorporating KEYNOTE-024 utilities directly, the ratio of utilities for the pembrolizumab monotherapy as compared to the chemotherapy arm in KEYNOTE-024 was first estimated for each health state and then multiplied by the utility values assumed for the corresponding health state for patients in the chemotherapy arm in KEYNOTE-407. Effectively, this method normalises the estimated utility values for pembrolizumab monotherapy patients so that the relationship in utilities relative to chemotherapy patients is preserved when comparing to KEYNOTE-407 values (

Table 67).

Table 67: Estimation of EQ-5D Utility Values for Patients Treated with Pembrolizumab Monotherapy

Utility Category	Pembrolizumab in KN024 (95% CI)	Chemotherapy in KN024 (95% CI)	KN024 Ratio (Pembro:Chemo)	Modeled Values for Pembrolizumab Monotherapy (95% CI)
Time to Death				
≥360**	0.860	0.837	1.03	**0.865**
[180, 360)	0.778	0.770	1.01	**0.822**
[30,180)	0.689	0.711	0.97	**0.714**
<30	0.699	0.609	1.15	**0.652**
Progression Status				
PF	0.851	0.811	1.05	**0.863**
PD	0.742	0.745	1.00	**0.739**
By AE Status in PF Patients				
With Grade 3+ AEs	0.820	0.764	1.07	**0.900**
Without Grade 3+ AEs	0.856	0.830	1.03	**0.841**
Difference (Utility decrement)	0.041	0.089		**0.059**

The time to death utility data shows there was no evidence to suggest a statistically significant difference in EQ-5D scores by treatment arm, with the potential exception of the time to death interval of >360 days, and therefore, scores from the pooled treatment groups for each state were used in the model.

The level of EQ-5D compliance through time is presented in

Table 68.

Table 68. Compliance of EQ-5D by visit and by treatment (FAS Population) [129]

Treatment Visit	Category	Pembrolizumab combination	SoC
		N = 402	N = 200
Baseline	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 3	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 6	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 9	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 12	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 15	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 18	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 27	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 36	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 45	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]

*: Compliance is the proportion of subjects who completed the PRO questionnaire among these who are expected to complete at each time point, excluding these missing by design.
Missing by design includes:death, discontinuation, translations not available, and no visit scheduled.
Database Cutoff Date: 03APR2018

UK preference-based scores were used for all patients analysed from the KEYNOTE-407 clinical trial. The UK scoring functions were developed based on the time trade-off (TTO) technique [130]. The estimated utilities are presented in Table 69 and

Table 70 below.

Table 69: EQ-5D health utility scores by time-to-death [4]

Time from EQ-5D Assessment Date to Death or Censoring Date (days)	Pembrolizumab combination					SoC					Pooled				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
≥ 360	[redacted]														
[180, 360)	[redacted]														
[30, 180)	[redacted]														
<30	[redacted]														

n† = Number of patients with non-missing EQ-5D score

m‡ = Number of records with non-missing EQ-5D score

EQ-5D score during baseline is not included

Database cut-off date: April 2018

Table 70: EQ-5D health utility scores by progression status

	Pembrolizumab combination					SoC					Pooled				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
Progressive	[redacted]														

n† = Number of patients with non-missing EQ-5D score

m‡ = Number of records with non-missing EQ-5D score

EQ-5D score during baseline is not included

Database cut-off date: April 2018

B.3.4.2 Mapping

Not applicable as HRQoL was derived from the KEYNOTE-407 EQ-5D data.

Utilities were evaluated using EQ-5D directly from patients from the KEYNOTE-407 trial, which is consistent with the NICE reference case [110].

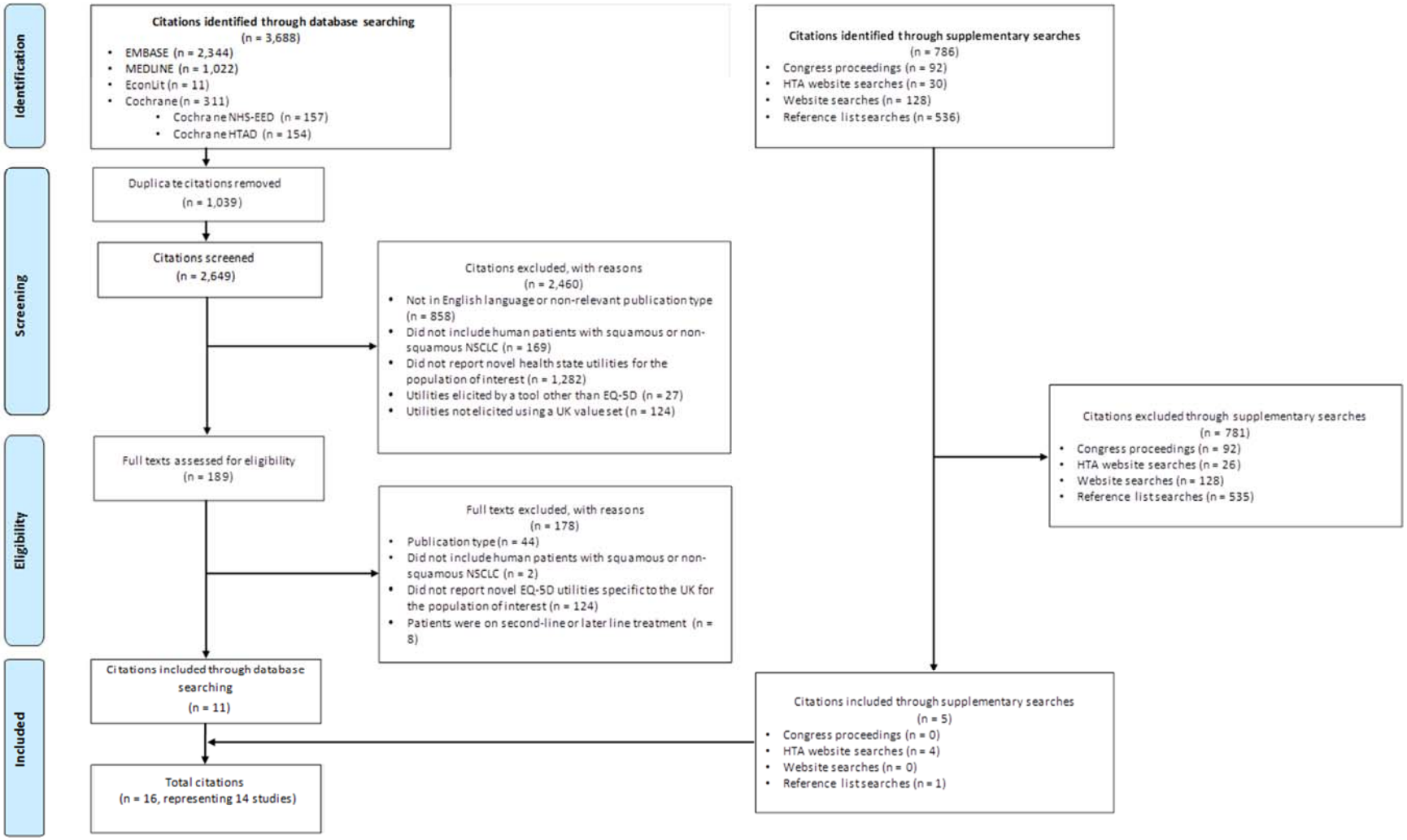
B.3.4.3 Health-related quality-of-life studies

In line with the NICE guide to the methods of technology appraisal [110], a systematic review of the literature was conducted to identify relevant studies reporting utility values. This was part of a single review that was performed to identify relevant studies in squamous NSCLC that included economic evaluations, studies reporting EQ-5D utility values and studies reporting cost and resource use data as described in section B.3.1. Full details of the search strategy and databases searched for HRQoL and utilities can be found in Appendix G. The eligibility criteria are presented in table below.

Consistent with the decision problem, the population of interest in this systematic search was metastatic NSCLC patients receiving first-line treatment; studies were the treatment line was unclear were also included but second or further line treatment studies were excluded. In terms of the outcomes, the studies were included only if they reported novel EQ-5D utility values derived from the UK preference value set. This is in line with the NICE reference case which suggests that the EQ-5D is the preferred measure of HRQoL in adults and that the UK value set should be used to generate health-related utility values. In order to avoid missing any relevant studies due to the outcomes inclusion criteria, studies that had a UK author or studies from multicentre trials that mentioned QALYs, EQ-5D or utilities were carried to the full-stage review to be thoroughly investigated before exclusion.

The database, internet and hand searches identified 4,474 records. In total, data from 16 citations were extracted (representing 14 studies) that reported utility values in the first-line or unknown line setting. Details of characteristics of the identified studies can be found in Appendix H. PRISMA flow diagram is presented in Figure 29 below:

Figure 29. PRISMA flow diagram for the EQ-5D utility studies



Utilities based on time-to-death used in the base case of the cost-effectiveness model allow a better reflection of the HRQoL experienced by patients through time. A similar approach was presented in NICE TA309 [131] where the manufacturer used utility values from the PARAMOUNT trial by treatment arm, progressed state and time to death. However, the values presented cannot be directly compared with the utility values from KEYNOTE-407 which do not incorporate the impact of progression on the time to death utilities. The time to death utility approach was also used and accepted by the committee in the recent TA for pembrolizumab in 1L NSCLC[94, 100] [redacted].

One publication was identified reporting time-to-death utilities and this was an HTA submission to Scottish Medicines Consortium (SMC) where high PD-L1 expressing patients were treated with pembrolizumab vs chemotherapy as a first-line treatment based on data from KEYNOTE-024 [132]. Utilities reported in the aforementioned SMC submission are higher than the utilities in KEYNOTE-407 which is to be expected in the wholly squamous NSCLC population in KEYNOTE-407 with the downward trend towards death being consistent. Another economic evaluation to NICE was identified for the same indication based on KEYNOTE-024 data however, the utilities were redacted from the published version of the submission therefore the systematic literature review identified it as supplementary to the SMC HTA submission. The utility from the latest data cut of KEYNOTE-024 has been used to model utility in the CE model used in this submission. The values have been normalised for differences in patient characteristics between studies as described in section B.3.4.1.

Overall, the pre- and post- progression utility values from the KEYNOTE-407 trial are in line with the utilities observed in the published literature, as the pre-progression EQ-5D values were higher than the post-progression values, suggesting a worsening of HRQoL after disease progression.[133] [134]

Two of the studies reported utilities pre- and post-reduction of the active drug dose [135, 136]; these seem to increase post-reduction however they are not comparable to the KEYNOTE-407 utilities. Also, the study population in these two studies refers to patients with EGFR+m NSCLC while the EGFR mutation in squamous NSCLC is very rare.

Three studies [137-139] reported utilities in multiple time points. Khan et al [138] presented utilities for the first line use of erlotinib in patients with advanced NSCLC; the time points are: baseline, 3, 6 and 12 months and the utilities are 0.56, 0.61, 0.66 and 0.58. The utilities are significantly lower compared to KEYNOTE-407 because the population in the study by Khan is unsuitable for chemotherapy; health is expected to be poorer in these patients therefore

the lower utility values are not surprising. Overall utilities are also presented but the line of treatment not clear. Meregaglia et al. [139] also reported EQ-5D utilities on various timepoints however the investigation focused on cachexia, the line of treatment is not clear and the relevance to the cost-effectiveness model is limited.

Two economic evaluation studies included in the systematic review estimated progression free utility values however the population in both studies were explicitly non-squamous.

None of the studies reported utility values associated with adverse events, except form Khan et al 2015 who reported utilities for a sub-population within the study that developed rash during the first treatment cycle.

Even though all of the studies included had the EQ-5D health state descriptions elicited directly from patients, using the UK values set, none of them was deemed to be comparable with KEYNOTE 407 for consideration for use within the health economic model. Further details of these studies are presented in Appendix H.

B.3.4.4 Adverse reactions

The impact of AEs on HRQoL was assessed by examining the EQ-5D health utilities of patients who experienced AEs (grade 3-5) compared to those who did not experience AEs in the progression-free health state.

For this assessment, the time points associated with grade 3-5 AEs for each patient were identified. EQ-5D scores collected at these time points were then used to estimate the utility of the progression-free state with grade 3-5 AEs. EQ-5D scores collected at other time points were used to estimate the utility associated with the progression-free health state in the absence of grade 3-5 AEs. EQ-5D data from the latest data cut (April 2018) was used. The utility values for patients experiencing grade 3-5 AEs were lower ([redacted]) than those of patients not experiencing grade 3-5 AEs ([redacted]); see Table 71). Additionally, patients who were progression-free and had not experienced grade 3-5 AEs reported higher utility values when treated with pembrolizumab combination compared to SoC [redacted], respectively).

In the base case, the average disutility per patient experiencing grade 3-5 AEs was [redacted] for patients treated with pembrolizumab combination and [redacted] for those treated with SoC.

It has been assumed for the purposes of the modelling that any impact of AEs on HRQoL is expressed in terms of a disutility of AEs applied based on AE incidence rates and the corresponding mean duration across them (i.e. [redacted] days of duration across grade 3+ AEs, as estimated from KEYNOTE-407).

Table 71: Utility values for individuals with and without Grade 3+ AEs in the KN407 clinical trial

	Pembrolizumab combination					SoC					Pooled				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
During Grade3+ AEs while Progression Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression Free without Grade3+ AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n† = Number of patients with non-missing EQ-5D score

m‡ = Number of records with non-missing EQ-5D score

EQ-5D score during baseline is not included

Database cut-off date: April 2018

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

HRQoL in the base case scenario is based upon time to death as the utility values derived from the KEYNOTE-407 trial were more sensitive than the pre-and post- progression utility values. EQ-5D analyses based on KEYNOTE-407 data showed that patients who had progressive disease experienced a lower HRQoL than those in the pre-progression health state. However, due to high level of crossover from the SoC arm to the pembrolizumab arm and due to the limitations with the data collected post-progression, progression related utilities do not show a large difference between pre and post-progression utilities, indicating that progression status is unlikely to be sufficiently reflective of changes in quality of life. When time-to-death was considered, HRQoL decreased over time as patients progressed closer to death. Therefore, to capture HRQoL more appropriately, the time-to-death utility values were further divided according to four categories (i.e. 360 or more days to death, 180 to 360 days to death, 30 to 180 days to death or under 30 days to death).

In the cost-effectiveness model, a constant value for HRQoL is applied in each cycle taking into account either time to death or progression-based health states. An age-related utility decrement of 0.0044 was applied per year, from the age of 65 until 75, to reflect the natural decrease in utility associated with increasing age [140].

The annual age-related utility decrement applied in the model is based on the age and gender-specific UK general population utility norms presented by Ara and Brazier et al.[140], which reported average utility values for males and females under 25, 25-34, 35-44, 45-54, 55-64, 65-74 and 75+ respectively. It was assumed that the utilities for 75+ reported by Kind et al. (0.72 and 0.70 for males and females, respectively) apply to all patients who are 75 years and above. Therefore, no further age-related decrement in utility was applied in the model for patients aged over 75 years. This means that patients aged 75 and above had the same age-related utility decrement in the cost-effectiveness model.

No health effects on patients were excluded from the cost effectiveness analysis. However, the impact of pembrolizumab combination vs. SoC on carers has not been included in the cost-effectiveness assessment due to the unavailability of data to incorporate this into the model.

The utility values chosen for the cost-effectiveness model are presented in Table 72.

Table 72: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
≥360*	[redacted]	[redacted]	Section B.3.4: B.3.4.1 Health-related quality-of-life data from clinical trials (page 150-158)	Utility values from KEYNOTE-407 (Data cut: April 2018), in line with NICE reference case[110, 141]
[180, 360)	[redacted]	[redacted]		
[30, 180)	[redacted]	[redacted]		
<30	[redacted]	[redacted]		
Disutility per patient experiencing grade 3-5 AEs	Pembrolizumab combination: [redacted] SoC: [redacted]		Section B.3.4: Adverse reactions (page 161)	
** This group also includes patients whose death dates were censored and report EQ5D ≥ 360 days.* *** Utilities from KEYNOTE-407 are pooled utilities*				

A clinical expert assessed the applicability of the health state utility values estimated from KEYNOTE-407 and these were thought to be reasonable.

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

A systematic literature review was conducted to identify costs and resource use associated with the first line treatment of advanced NSCLC in the UK. This was part of the single systematic review described in section B.3.1.

The population criteria were limited to patients who received first line treatment or where the treatment was unclear but not limited to the squamous NSCLC population because literature for the squamous only population is scarce. The eligibility criteria considered in the review are presented in Table 73. Eligibility criteria for cost and resource use are in Table 73 below. Details of the systematic review conducted as part of the appraisal for the identification of relevant cost and health care resource use data to populate the model can be found in Appendix G. The parameters used to estimate cost effectiveness has been presented as part of Appendix L.

Table 73. Eligibility criteria for cost and resource use

Domain	Costs and resource use	
	Inclusion Criteria	Exclusion Criteria

Population	Patients with squamous or non-squamous NSCLC receiving first-line treatment or where the treatment line was unclear	Individuals without NSCLC, NSCLC patients treated in the second or later line and populations where outcomes are not presented separately for the patients of interest
Intervention(s)	Any or none	-
Comparator(s)	Any or none	-
Outcomes	Novel direct costs and resource use Data must be relevant to the UK NHS and PSS or Irish HSE or DoH*, and of relevance to an economic model of pembrolizumab In addition, data must have been collected within the last 10 years for the study to be eligible for inclusion	Studies not presenting original, relevant cost/resource use data for the population of interest (e.g. indirect costs; non-UK/Irish costs only), or studies presenting data collected more than 10 years ago
Study design	Any original research study, including budget impact models and cost-of-illness studies	-
Publication type	• Journal articles presenting original research • Systematic reviews of relevant primary publications (these were included at the title/abstract stage and used for the identification of any additional primary studies not identified through the database searches. They were then excluded during the full-text review stage unless they reported primary, original research themselves) • HTAs • Congress abstracts published in or after 2016	
ther considerations	Studies conducted in the UK or Ireland only* English language Human subjects	Studies not conducted in the UK or Ireland Non-English language articles Articles not on human subjects

**Given the potential for a future submission in Ireland, the published UK search filter was adapted to cover the Irish perspective as well as UK. The eligibility criteria were adapted accordingly.*

***Abbreviations:** DoH: Department of Health;; HSE: Health Service Executive; HTA: health technology assessment; NHS: National Health System; NSCLC: non-small cell lung cancer; PSS: Personal and Social Services; UK: United Kingdom.*

From 4,474 citations identified, 18 met the eligibility criteria for inclusion, 3 of which were economic evaluations submitted to NICE and 3 were reference list searches. The PRISMA flow diagram is presented below. The studies are summarised in Appendix I.

Although all studies included, reported data relevant to the UK practice, one study reported costs in Euro currency [142]; 12 of the studies did not report any relevant novel costs. Two studies reported costs related to treatment costs and more specifically to platinum doublet chemotherapy [143], [144] but only one of them studied advanced metastatic patients [144], estimating the mean cost to £1,531.40 per patient per month (cost year 2014/2015).

In terms of administration and AE costs, some of the studies report estimates that do not have the level of granularity to inform our cost effectiveness model [144], [145],[142]

In terms of resource use, all 3 economic evaluations presented pre- and post-progression use of certain resources however, in 2 of them (TA 500, TA536) the population studied is NSCLC with ALK mutations which are very rare in squamous population. The third, (TA 411), reports information potentially relevant to the cost effectiveness model however was in the EGFR positive population. Data that were deemed relevant to the CE model have been used.

It should be noted that while not eligible for inclusion in the current SLR, one publication was highlighted as particularly a useful resource; Brown et al. 2013 which presented a systematic literature review of first-line chemotherapy for NSCLC.[146] This SLR, along with all other identified SLRs and HTAs, was manually hand-searched to identify any further relevant original research publications that had not already been detected. No relevant publications were identified through hand-searching of Brown et al. 2013 that had not been identified through other sources.

B.3.5.1 Intervention and comparators' costs and resource use

Drug costs

The drug acquisition costs per treatment are presented below, with the unit costs for comparators being taken from the electronic market information tool (eMit [147]) which provides information about prices for generic drugs based on the average price paid by the NHS over the last four months. If comparators' drug costs were not available from eMIT, the costs from the British National Formulary (BNF) [148] were used.

Pembrolizumab

As per the anticipated licence, the model uses a 200mg fixed dose of pembrolizumab, administered as a 30 minute IV infusion every three weeks (Q3W) (see the Summary of Product Characteristics [SmPC] in Appendix C). The list price of a 100mg vial is £2,630.00.

Therefore, the drug cost for pembrolizumab per administration is £5,260 based on two 100mg vials using the list price. [redacted]

Comparators and combination drugs

Drug acquisition costs for individual drugs included in the platinum-based combination therapies were taken from eMit[147]. When multiple vial/package sizes were available, the cheapest price per mg was applied as a conservative assumption. The costs of concomitant medications for patients receiving doublet chemotherapy (e.g. steroids, paracetamol etc.) were not taken into consideration as the costs are trivial and unlikely to affect the results.

Dosing for the individual drugs was based on the KEYNOTE-407 protocol [36] whenever available. Dosing for the remaining drugs not included in KEYNOTE-407 was based on SmPC or Brown et al [149] [150] [108] (2013). Drug costs per administration were calculated based on the body surface area (BSA), which was assumed to be 1.86m^2 based on a mean BSA from the male and female patients recruited at European sites in KEYNOTE-407 (see

Table 74). As a conservative assumption, full vial sharing (i.e., no wastage) is assumed for the administration of all comparator drugs.

Table 74: Baseline body surface area (BSA) of patients recruited at European sites in KEYNOTE-407

	Mean BSA in m^2 [151]	% of patients[151]
Female	[redacted]	[redacted]
Male	[redacted]	[redacted]
Total	[redacted]	[redacted]

Table 75: Dosing, frequency of infusion and unit costs per administration for comparator drugs

Drug	Dosing per administration	Frequency of administration	Total dose	Cost per mg	Cost per administration (assuming no wastage)	Reference for dosing	Reference for drug costs

Pembrolizumab	200mg	Q3W	200mg	£26.30	£5260	SmPC [152]	BNF [148]
Paclitaxel	200mg/m^2	Q3W	362mg	£0.07	£24.40	KEYNOTE 407	eMit[147]
Nab-Paclitaxel	100mg	Q1W	100mg	£2.46	£1,372.68	KEYNOTE 407	BNF [148]
Carboplatin	400mg/m^2	Q3W	724mg	£0.04	£30.97	KEYNOTE-407	eMit[147]

* Q1W, every week; Q3W, every three weeks

The drug costs of the overall combination therapy used in the economic model are the weighted sum of the drug costs of the individual combination treatments where weights were based on the KEYNOTE-407 in the base case and UK market shares for the distribution of paclitaxel/nab paclitaxel in scenario analysis. The distribution of carboplatin vs. cisplatin use within platinum chemotherapy regimens in stage IV squamous NSCLC (including all treatments listed in the scope other than vinorelbine plus platinum since a comparison could not be made versus this regimen [1]) as per UK market share are utilised for these indirect treatment comparators (

Table 76). Table 77 summarises the drug costs per administration for the comparators used in the economic model.

Table 76: Distribution of the use of therapies

	KEYNOTE-407 (base case) [4]	UK market shares distribution of carboplatin vs. cisplatin use within platinum chemotherapy regimens in stage IV squamous NSCLC [111]	UK market share paclitaxel/nab paclitaxel scenario analysis
Gemcitabine/carboplatin	n/a	69%	0%
Gemcitabine/cisplatin	n/a	31%	0%
Nab-Paclitaxel/carboplatin	39.9%	0%	0%
Nab-Paclitaxel/cisplatin	n/a	0%	0%
Paclitaxel/carboplatin	60.1%	93%	100%
Paclitaxel/cisplatin	n/a	7%	0%
Docetaxel/carboplatin	n/a	63%	0%
Docetaxel/cisplatin	n/a	37%	0%
% Total	100%	100%	100%

Table 77: Summary of the drug costs per administration for the comparator used in the base case

	Overall population

SoC: Car plus Pac/Nab-Pac	£576.69

Number of administrations required, unit costs and total drug costs per treatment per cycle

As per the licence, patients treated with pembrolizumab are to be treated until disease progression is confirmed. To estimate the duration of treatment in the pembrolizumab combination and SoC arms, time on treatment (ToT) data from the KEYNOTE-407 April 2018 data-cut was used, to reflect both early discontinuation caused by AEs and other reasons for discontinuations before progression in addition to the additional weeks of treatment that some patients may receive until confirmation of progression. See Appendix I for further details regarding the use of ToT data in the model.

In the base case model, a maximum treatment duration of 2 years was assumed for pembrolizumab, in line with the KEYNOTE-407 protocol [36] and the current recommendations for the use of pembrolizumab for the treatment of patients with advanced NSCLC [94, 100, 109]. A maximum treatment duration of 12 weeks (i.e., 4 cycles for the platinum-based therapies administrated every 3 weeks) was used for the comparator platinum-based therapies to reflect the protocol of KEYNOTE-407 [36] and clinical practice in England. The average number of cycles received in the comparator arm per patient in KEYNOTE-407 was 3.4 and 8.7 (Paclitaxel and nab-paclitaxel respectively both with 3.5 carboplatin) and 3.6 and 9.0 (paclitaxel and nab paclitaxel respectively plus 3.7 and 3.5 carboplatin) in the pembrolizumab combination.

For patients on treatment, adjustments were made based on the actual proportion of patients receiving the planned dose within KEYNOTE-407. For this, data regarding dose interruption occurring within KEYNOTE-407 was analysed and incorporated into the model per administered cycle of pembrolizumab and comparators. These analyses showed that, on average, 93.5% of patients on pembrolizumab combination and 98.1% of patients on overall platinum-based chemotherapy received their planned doses.

B.3.5.2 Administration costs

Pembrolizumab combination

Given the time required for the administration of pembrolizumab is 30 minutes, the Healthcare Resource Groups (HRG) code for 'simple parenteral chemotherapy – outpatient' SB12Z based on the National Tariff Chemotherapy Regimens list [153] and latest NHS

reference costs 2016-2017 [154] was used to reflect administration costs for pembrolizumab monotherapy.

For carboplatin/paclitaxel, the HRG code SB14Z for "Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance" [153] but for carboplatin/nab-paclitaxel 2 x SB15Z "Deliver subsequent elements of a chemotherapy cycle" were added since this is given subsequently on two additional days of the cycle [155] [156]. The administration burden for paclitaxel/nab-paclitaxel was weighted as per its use in KEYNOTE-407 [4]. This was added to the aforementioned pembrolizumab monotherapy administration cost.

It should be noted that the administration cost for pembrolizumab combination is based on the time on treatment curve which means that conservatively, the administration costs of the chemotherapy part of the combinations administration cost has been applied more than would be in practice since a patient would not have more than 4 cycles of chemotherapy followed by further pembrolizumab monotherapy at a lower administration cost burden.

Platinum-based combination therapy

The administration costs required for platinum-based therapies were based on the National Tariff Chemotherapy Regimen List 2017-18 [153]. The unit cost per cycle of chemotherapy administrated was taken from the National Reference Costs 2016/17 [154].

Table **78** summarises the administration costs used in the cost-effectiveness model.

Table 78. Administration costs of pembrolizumab and platinum-based chemotherapy

	Assumptions	**Unit costs**	**Reference**
Pembrolizumab + carboplatin+paclitaxel/nab-paclitaxel	1 x SB12Z (outpatient) plus 1 x SB14Z (outpatient) – for pembrolizumab + carboplatin + paclitaxel 1 x SB12Z (outpatient) plus 1 x SB14Z (outpatient) + 2 x SB15Z (outpatient)	£607.52	National tariff chemotherapy regimen list 2017-18 [153] and weighted by share in KEYNOTE-407
Pembrolizumab mono	1 x SB12Z (outpatient)	£173.99	National tariff chemotherapy regimen list 2017-18 [153]

Table 79 summarises the drug administration costs for the comparators used in the economic model.

Table 79. Summary of the drug administration costs for the comparator used in the base case

	All
SoC: Carb plus Pac/Nab-Pac	£433.52

B.3.5.3 Costs associated with PD-L1 testing

The anticipated license for pembrolizumab in combination with carboplatin plus paclitaxel/nab-paclitaxel is for the first line treatment of advanced squamous NSCLC in adults. PD-L1 testing is routine in the NHS for all new diagnoses of NSCLC, and since every patient considered by the model should receive the test, its cost does not differ between strategies. Therefore it was excluded from consideration in the cost-effectiveness analysis. This was in line with previous NICE submission review. [157]

B.3.5.5 Health-state unit costs and resource use

The main source of resource utilisation per health state used in this submission was the Brown et al study, which compares regimens currently approved by NICE and licensed across Europe for the systemic treatment of patients with advanced NSCLC [108]. From the studies evaluated within the systematic review, MSD concludes that this study provides the most balanced and appropriate evaluation of cost and resource use given its relevance to the UK setting, recent publication and broad inclusion of treatment strategies in advanced NSCLC. Where possible and applicable to the population being assessed here, health state resource utilisation have been included from studies identified in the corresponding SLR.

Monitoring and disease management costs

There are three health states included in the model - Progression free (PFS), Progressed (PD) and death.

Patients incur disease management costs for as long as they remain on treatment, and potentially longer. The unit costs of treatment are consistent over cycle lengths; however the frequency of resource consumption per cycle varies depending on the health state.

Table 53 shows the resource use for monitoring and disease management in the progression-free and progressed health state. Based on the definitions for health states used in the Brown et al study [108] , PFS costs from Brown et al. were applied during first-line chemotherapy and for patients modelled to receive a second-line therapy following first-line

treatment discontinuation. PD costs were only applied when no active treatment is received following 1st line therapy discontinuation.

Table 81 presents the unit costs for individual resource use items, which were updated based on the NHS reference costs 2016-2017 and the Personal and Personal and Social Services Research Unit (PSSRU) 2017 report [154{Curtis, 2017 #52}]. The estimated per week monitoring and disease management costs were £89.53 and £144.53 respectively for the PFS and PPS periods.

Table 80: Resource use frequency for progression-free and progressed health states

Resource	PFS	PPS	Unit	Source quoted in Brown 2013
Outpatient visit	17.33	17.33	per annum	TA411 [95]
Chest radiography	17.33	17.33	per annum	TA411 [95]
CT scan (chest)	0.62	0.24	per annum	Big Lung Trial[158]
CT scan (other)	0.36	0.42	per annum	Big Lung Trial[158]
ECG	1.04	0.88	per annum	Big Lung Trial[158]
Community nurse visit	8.7	8.7	visits (20 minutes) per patient	Appendix 1 of NICE Guideline CG81, Marie Curie report [159, 160]
Clinical nurse specialist	12	12	hours contact time per patient	Appendix 1 of NICE Guideline CG81[160]
GP surgery	12	0	consultations per patient	Appendix 1 of NICE Guideline CG81
GP home visit	0	26.09	per annum (fortnightly)	Marie Curie report[159, 160]
Therapist visit	0	26.09	per annum (fortnightly)	Appendix 1 of NICE Guideline CG81[160]
Macmillan nurse	0	0		Marie Curie report[159]
Drugs/equiptment	0	0		Marie Curie report[159]
Location of terminal care	0	0		Office for National Statistics death tables 5.2 [161]

* PFS, progression free state; PPS, post-progression state; GP, general practitioner; CT, computerised tomography; ECG, electrocardiogram; NICE, The National Institute for Health and Care Excellence

Table 81. Unit costs of disease monitoring and supportive care

Resource	Unit cost	Unit	Source
Outpatient follow-up visit	£128.00	per visit	NHS Reference Costs 2016–2017, Consultant Led, Non-Admitted Face to Face Attendance, First, 800 clinical oncology[154]
Chest radiography	£27.22	per case	NICE technology appraisal TA199; TAG report, p.328 (£24.04 in 2009) [162]
CT scan (chest)	£110.00	per case	NHS Reference Costs 2016–2017, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast) [154]
CT scan (other)	£118.00	per case	NHS Reference Costs 2016–2017, Diagnostic Imaging, Outpatient, HRG code RD26Z (three areas with contrast) [154]
ECG	£334.00	per case	NHS Reference Costs 2016–2017, 800 Clinical

			Oncology, Outpatient, HRG code EY51Z[154]
Community nurse visit	£62.00	per hour	PSSRU 2017, p.142: Cost per hour of patient-related work Band 8a[163]
Clinical nurse specialist	£74.00	per contact hour	PSSRU 2017, p.142: Cost per contact hour Band 8b[163]
GP surgery visit	£38.00	per visit	PSSRU 2017[163], p.145: Cost per patient contact lasting 11.7 minutes, including direct care staff costs (including qualifications)
GP home visit	£85.44	per visit	PSSRU 2017, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel[163]
Therapist visit	£45.00	per hour	PSSRU 2017, p.159: Cost per hour for community occupational therapist (including training) [163]

* GP, general practitioner; CT, computerised tomography; ECG, electrocardiogram; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; NICE, The National Institute for Health and Care Excellence; HRG, Healthcare Resource Groups; TAG, Technology Assessment Group

Cost of terminal care

A one-off cost is applied to those patients at the moment of dying to reflect the cost of terminal care. The resource consumption reflects treatment received in various care settings, and is also based on the values used in the Brown et al study for consistency [108]. The estimated one-off terminal costs were £4,404.26 and are assumed to be the same for all treatment arms (see Table 82).

Table 82: Unit costs of terminal care patients (based on Brown et al study) [108]

Resource	Unit cost	Number of consumption	% of patients in each care setting	Assumptions / Reference
Community nurse visit	£62.00 per hour	28.00 hours	30%	PSSRU 2017, p.169: Cost per hour of patient-related work (including qualifications) [163]
GP Home visit	£85.44 per visit	7.00 visits	30%	PSSRU 2017, p.177-178: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel[163]
Macmillan nurse	£49.36 per hour	50.00 hours	30%	Assumed to be 66.7% of community nurse cost[108]
Drugs and equipment	£563 per patient	Average drug and equipment usage	30%	The value used in Brown et al' s study (2013, Marie Curie report figure of £240 increased for inflation) was inflated to 2016/17 using the PSSRU HCHS index[108, 159]
Terminal care in hospital	£3,737.05 per episode	1 episode (9.66 days)	62%	NHS Reference Costs 2016–2017, Non-Elective Long Stay and Non-Elective Excess Bed Days, Weighted sum of HRG code DZ17L (Respiratory Neoplasms with Multiple Interventions, with CC Score 10+), DZ19P (Respiratory Neoplasms with Single Intervention, with CC Score 10+) and DZ17T (Respiratory Neoplasms without Interventions, with CC Score 8-12) by activity Assumed that unit cost is = £3,606.87 + 0.92 excess days at £267.74 per day[108, 154]
Terminal care in hospice	£4,671.32 per episode	1 episode (9.66 days)	7.1%	Assumed 25% increase on hospital inpatient care[108]
Total cost	£4,404.24 (one-off cost)			

* GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; HCHS, Hospital and Community Health Service; NICE, The National Institute for Health and Care Excellence; HRG, Healthcare Resource Groups

B.3.5.6 Adverse reaction unit costs and resource use

A description of the AEs included in the model and the corresponding frequencies are presented in section B.3.3.

The unit costs related to the management of AEs were mainly derived from the Brown et al study and from the previous NICE STA submissions [108]. When unit costs were not available or the management costs were trivial, zero cost was applied. All unit costs were inflated to 2016/17 prices using the hospital and community health services (HCHS) index published by PSSRU for 2017 [163] Table 83 below presents the unit costs per AE for which costing was applied in the cost-effectiveness model.

Table 83: Unit cost per AE used in the de novo model

Adverse Event	Unit costs	Reference
Nausea	£998.38	Brown et al, 2013 (inflated to 2016/17 using PSSRU inflation indices)
Anaemia	£2,692.61	TA428, 2016 (inflated to 2016/17)
Fatigue	£2,855.25	Brown et al, 2013 (inflated to 2016/17 using PSSRU inflation indices)
Decreased appetite	£0.00	TA428, 2016 (inflated to 2016/17 using PSSRU inflation indices)
Constipation	£0.00	Assumed to be zero
Diarrhoea (grade 2)	£456.66	TA428, 2016 (inflated to 2016/17 using PSSRU inflation indices)
Diarrhoea (grade 3-4)	£998.38	Brown et al, 2013 (inflated to 2016/17 using PSSRU inflation indices)
Dyspnoea	£588.98	TA403 (inflated to 2016/17 using PSSRU inflation indices)
Vomiting	£813.47	TA192, 2010 (inflated to 2016/17 using PSSRU inflation indices)
Back pain	£0.00	Assumed to be zero
Arthralgia	£0.00	Assumed to be zero
Neutropenia	£120.99	Brown et al, 2013 (inflated to 2016/17 using PSSRU inflation indices)
Oedema peripheral	£0.00	Assumed to be zero
Blood creatinine increased	£0.00	Assumed to be zero
Alanine aminotransferase increased	£637.03	TA347, 2015 (inflated to 2016/17 using PSSRU inflation indices)
Dizziness	£0.00	Assumed to be zero
Rash	£127.21	Brown et al, 2013 (inflated to 2016/17 using PSSRU inflation indices)
Asthenia	£2,855.25	Brown et al, 2013 (inflated to 2016/17 using PSSRU inflation indices)
Chest pain	£0.00	Assumed to be zero
Stomatitis	£0.00	TA428, 2016
Hyponatraemia	£0.00	ID760, 2015

Adverse Event	Unit costs	Reference
Thrombocytopenia	£782.31	TA406, 2016 (inflated to 2016/17 using PSSRU inflation indices)
Neuropathy Peripheral	£0.00	Assumed to be zero
Abdominal pain	£0.00	TA395
Aspartate aminotransferase increased	£364.64	TA347, 2015 (inflated to 2016/17 using PSSRU inflation indices)
Peripheral Sensory Neuropathy	£0.00	Assumed to be zero
Pyrexia	£261.00	NHS reference costs 16/17 WJ07B Fever of Unknown Origin with Interventions, with CC Score 0-3
Musculoskeletal pain	£0.00	Assumed to be zero
Pneumonia	£3,102.84	TA411, 2016 (inflated to 2016/17 using PSSRU inflation indices)
White blood cell count decreased	£577.66	TA428, 2016 (inflated to 2016/17 using PSSRU inflation indices)
Haemoptysis	£0.00	Assumed to be zero
Pain in extremity	£0.00	Assumed to be zero
Cough	£0.00	Assume to be zero
Myalgia	£0.00	Assumed to be zero
Pruritis	£0.00	Assumed to be zero
Upper respiratory tract infection	£171.14	Assume the same as lower respiratory tract infection: Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs (ID939) inflated to 16/17 using PSSRU
Leukopenia	£0.00	TA406, 2016
Epistaxis	£0.00	Assumed to be zero
Neutrophil Count Decreased	£577.66	TA428, 2016 (inflated to 2016/17 using PSSRU inflation indices)
Pneumonitis	£3,102.84	Assumed to be same as pneumonia based on TA395 (inflated to 2016/17 using PSSRU inflation indices)
Febrile neutropenia	£7,045.41	Brown et al, 2013(inflated to 2016/17 using PSSRU inflation indices)
Bronchitis	£171.14	Assume the same as lower respiratory tract infection: Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs (ID939) inflated to 16/17 using PSSRU
Platelet Count Decreased	£577.66	TA428, 2016 (inflated to 2016/17 using PSSRU inflation indices)
Weight decreased	£0.00	Assume same as decreased appetite - TA428, 2016
Hypothyroidism	£0.00	Assumed to be zero
Hypokalaemia	£465.00	NHS reference costs 16/17 KC05G: Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+
Hypomagnesaemia	£465.00	NHS reference costs 16/17 KC05G: Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+
Hyperthyroidism	£0.00	Assumed to be zero
Headache	£0.00	Assumed to be zero
Paraesthesia	£0.00	Assumed to be zero
Hypotension	£0.00	Assumed to be zero

Adverse Event	Unit costs	Reference
Hypocalcemia	£465.00	NHS reference costs 16/17 KC05G: Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+

* GP, Personal Social Services Research Unit; WBC, white blood cell.

B.3.5.7 Miscellaneous unit costs and resource use

Costs associated with subsequent therapies received by patients after treatment discontinuation

The percentage of patients who receive subsequent lines of therapy after treatment discontinuation (27.4% for pembrolizumab combination and 51.9% for SoC) was estimated from the KEYNOTE-407 trial [4]. Analogously, the proportion of pembrolizumab monotherapy patients with squamous histology (n = 29) that discontinued treatment and went on to receive a subsequent therapy was 31.0% within KEYNOTE-024 [164].

The estimated distribution of specific treatments post-discontinuation from the trial data is shown in Table 84.

. The distribution of post-discontinuation treatments is calculated in a few steps.

- From among patients utilising a treatment post-discontinuation, three groups are identified based on those receiving following discontinuation: 1) Only PD-1/PD-L1 regimens; 2) Only chemotherapy regimens; 3) Both chemotherapy and a PD-1/PD-L1 regimen.
- The post-discontinuation treatment with the longest duration of use is identified. For the group receiving both chemotherapy and a PD-1/PD-L1 regimen, the therapy with the longest duration of use within each category (i.e., one regimen of each type) is selected.
- For simplicity, only individual treatments of longest duration utilised in at least 5% of patients in a given trial arm, from among those utilizing a post-discontinuation treatment, are explicitly modelled. However, if a treatment meets this criterion for inclusion within one trial arm, any use within another trial arm is incorporated, given the decision to include. The percentages of patients receiving any other specific treatment within the three post-discontinuation groups are redistributed among the modelled treatments to ensure that the total proportion receiving subsequent therapy in each arm, and each group, is aligned with the trial data.

- Within the model, 2L IO therapy following pembrolizumab combination or monotherapy has not been included as this would not represent UK clinical practice.

This approach was undertaken so as to capture the most important post-discontinuation therapies utilised, while also maintaining a manageable number of individual therapies to model. While the costs of subsequent therapies are separately included in the model, OS and PFS impacts are assumed to be already reflected within the OS and PFS KM data from the KEYNOTE-407 trial, without switching adjustment as for patients in the SoC arm, cross over adjustment was not implemented in the ITT population since 2L IO drugs are now thought to be standard of care. Note that many patients who discontinue treatment within the costing conducted do not receive a subsequent therapy. This is reflective of patients who are too sick to do so (i.e. death), and a zero cost is essentially assigned for this proportion of patients.

Table 84. Type and distribution of second line subsequent chemotherapies used in the economic model

Post-discontinuation regimen (dose)	Pembrolizumab + Chemotherapy Arm	Chemotherapy Arm	Pembrolizumab Monotherapy
Patients who received anti-PD1/PD-L1 therapy only			
Nivolumab (100 mg/m^2)		[redacted]	
Pembrolizumab (200 mg)		[redacted]	
Patients who received chemotherapy only		[redacted]	
Carboplatin (400 mg/m^2) + Gemcitabine (1250 mg/m^2)	[redacted]		[redacted]
Carboplatin (400 mg/m^2) + Paclitaxel (200 mg/m^2)	[redacted]	[redacted]	[redacted]
Cisplatin (75 mg/m^2) + Gemcitabine (75 mg/m^2)	[redacted]	[redacted]	[redacted]
Cisplatin (75 mg/m^2) + Paclitaxel (200 mg/m^2)	[redacted]	[redacted]	[redacted]
Docetaxel (75 mg/m^2)	[redacted]	[redacted]	[redacted]
Gemcitabine (1250 mg/m^2)	[redacted]	[redacted]	[redacted]
Vinorelbine (27.5 mg/m^2)	[redacted]	[redacted]	[redacted]
Patients receiving both an anti-PD1/PD-L1 therapy and chemotherapy sequentially			
Carboplatin (400 mg/m^2) + Gemcitabine (1250 mg/m^2)		[redacted]	
Cisplatin (75 mg/m^2) + Gemcitabine (75 mg/m^2)		[redacted]	
Docetaxel (75 mg/m^2)		[redacted]	
Gemcitabine (1250 mg/m^2)		[redacted]	
Nivolumab (100 mg/m^2)		[redacted]	
Pembrolizumab (200 mg)		[redacted]	
Vinorelbine (27.5 mg/m^2)		[redacted]	

Table 85 Average treatment duration for 2L therapies

Post-discontinuation regimen	Pembrolizumab + Chemotherapy	Chemotherapy Arm	Pembrolizumab Monotherapy
Patients who received anti-PD1/PD-L1 therapy only		[redacted]	[redacted]
Patients who received chemotherapy only	[redacted]	[redacted]	[redacted]
Patients receiving both an anti-PD1/PD-L1 therapy and chemotherapy sequentially			
Anti-PD1/PD-L1 therapy		[redacted]	
Chemotherapy		[redacted]	

The average one-off cost of subsequent treatment for each arm was calculated by weighting the proportions of patients receiving each subsequent treatment and the unit cost of each subsequent treatment (including drug cost and administration cost as described above), assuming the average duration of treatment as reported above in Table 85. Therapies with a confidential discount in place have been assumed at list price. Administration costs per cycle were assumed to be the same as in first line therapy described above.

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

B.3.6.1 Summary of base-case analysis inputs

A table summarising the full list of variables applied in the economic model is presented in Appendix L.

B.3.6.2 Assumptions

Table 86 below presents a summary of the clinical inputs and data sources used in the economic model, and Table 87 summarises the assumptions used in the economic model. The base-case cost-effectiveness analyses reflects the NICE reference case as closely as possible.

Table 86. Summary of clinical inputs and data sources used in the economic model

Clinical evidence and source	Brief description	Use in the model
KEYNOTE-407	Multicentre open-label, randomised, phase 3 trial of pembrolizumab 200 mg plus carboplatin AUC plus paclitaxel/nab-paclitaxel Q3W (n=278) versus placebo plus carboplatin AUC plus paclitaxel/nab-paclitaxel Q3W (SoC) (n=280) in adults with untreated, advanced NSCLC. Data cut: April 2018	• Used to derive the baseline patient characteristics (including average age, the proportion of males and weighted average BSA). • Patient level data were used to fit OS and PFS parametric curves for both pembrolizumab combination and SoC arms. • Base case presented: o ITT: Patient level data from the SoC arm was not used to perform crossover adjustments for the SoC OS as part of the base case since IO therapy has become SoC second line among the patient population in this appraisal. • OS KM data until week 52 was used to model OS in the first phase of the OS before real world SEER data were applied. • PFS KM data were used to model PFS in the first 26 weeks before parametric curves were applied. • Patient level data was used to calculate the proportions of patients actually receiving the planned doses for both pembrolizumab combination and SoC. • EQ-5D data collected in the trial were used to derive health state utility values (time-to-death utility values) used in the model. • ToT KM data up to 2 years was used to estimate treatment duration in the pembrolizumab combination arm, while KM data was used for ToT in the SoC arm since there was a maximum of 4 cycles given. • Used to derive the incidence of grade 3+ AEs and grade 2 diarrhoea and febrile neutropaenia (all grades) for both pembrolizumab combination and SoC. • Used to derive the proportion of patients receiving subsequent treatments for both pembrolizumab combination and SoC.
General population mortality[165]	Latest national life table in England & Wales providing age- and gender-specific general population mortality.	Applied throughout the modelled time horizon as background mortality (i.e., general population mortality is applied when modelled mortality is lower than the gender- and age- matching general population mortality).

Key: AE, adverse event; HR, hazard ratio; IV, intravenous; KM, Kaplan-Meier; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PFS, progression free survival; Q3W, every 3 weeks; RCT, randomised controlled trial; TPS, proportion of tumour cells staining for PD-L1.

Table 87: List of assumptions used in the economic model

Area	Assumption	Justification
Treatment pathway	Once patients' progress they receive subsequent therapies as experienced by patients in KEYNOTE-407.	The use of subsequent treatments as observed in KEYNOTE-407 trial is consistent with the OS efficacy inputs used in the model, which are based on patients receiving these subsequent treatments. No crossover adjustment is applied in the base case cost-effectiveness model to reflect current clinical practice in the ITT population.
Time horizon	30 years	The average age of patients in the model is 65. A lifetime horizon is in line with NICE reference case. Duration of 30 years is considered long enough to reflect the difference in costs and outcomes between pembrolizumab combination and SoC as assessed in this submission
Efficacy	Use unadjusted KM data for the first 52 weeks from KEYNOTE-407 trial to model OS for pembrolizumab combination and SoC followed by real world SEER data	The longest use of KM data possible from the trial plus real world registry data from SEER to extrapolate long term outcomes providing the most plausible long term survival estimate for SoC.
HRQoL	The quality of life of patients is appropriately captured by considering time to death utilities	Clinical opinion suggests there is a decline in HRQL in the final months of life of advanced NSCLC patients which may not appropriately be captured solely through the use of progression-based health state. This was supported by the feedback provided by the ERG of previous NICE oncology submissions, which supported the use of a disutility associated to o the terminal stage. Since there were limitations to using a combined approach (including both progression-based and time to death utilities), and given the limitations of the progression-based approach to reflect appropriately utilities post-progression, a time to death approach was considered in the base case. In sensitivity analyses, the impact of considering an alternative approach (i.e. progression-based only) was considered.
Safety	The incidence of AEs from KEYNOTE-407 trial was assumed to reflect that observed in practice	Assumption based on the results of the KEYNOTE-407 trial (i.e. grade 3-5 AEs (incidence≥5% in one or more treatment groups, considering any grade)). The same method and criteria were applied in recent NICE appraisals for previously treated advanced NSCLC patients (TA347, ID811) [101, 166].
Costs	Using NHS reference costs and published literature sources where possible.	As per previous NICE oncology submissions [101, 166].

B.3.7 Base-case results

The results of the economic model are presented in Table 88 below. In the base case reflecting the original submission, the estimated mean overall survival was 4.03 years with pembrolizumab combination and 1.76 years with SoC. At the end of the 30-year time horizon there were 2.02% patients still alive in the pembrolizumab combination cohort and 0.02% in the SoC cohort. Patients treated with pembrolizumab combination accrued 2.95 QALYs compared to 1.27 among patients in the SoC cohort.

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

Table 88 and Table 89 below presents the base case incremental cost-effectiveness results for the base case incorporating the aforementioned discount.

The results show given that data are immature, pembrolizumab combination has the potential to be cost-effective compared to SoC when considering a willingness to pay threshold of £50,000 per QALY with the corresponding incremental-cost-effectiveness ratio (ICER) when pembrolizumab combination was compared to SoC was £28,672 in the base case. These ICERs should be considered in the context of pembrolizumab meeting end of life criteria and utilised in combination with the existing technology.

Table 88: Base-case results versus trial comparator SoC (with existing discount)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SoC	£24,417	1.76	2.95	-	-	-
Pembrolizumab combination	£72,695	4.03	1.27	£48,278	1.68	£28,672
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 89: Base-case results versus NMA comparators (with existing discount)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Platinum + Paclitaxel	£22,002	1.77	1.27	-	-	-
Pembrolizumab combination	£72,695	4.03	2.95	£50,693	1.68	£30,156
Platinum + Docetaxel	£21,184	1.63	1.17	-	-	-
Pembrolizumab combination	£72,695	4.03	2.95	£51,511	1.78	£28,927
Platinum + Gemcitabine	£30,947	3.16	2.30	-	-	-
Pembrolizumab combination	£72,695	4.03	2.95	£41,748	0.66	£63,661
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

The estimates of the clinical outcomes included in the cost-effectiveness analysis (compared with the clinical trial results) and the tabulated, disaggregated results for the base case are presented in Appendix J.

B.3.8 Sensitivity analyses

B.3.8.1 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 mean values, distributions around the means and sources used to estimate the parameters are detailed in Appendix L.

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 90, and the corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 30 and Figure 31.

Table 90: Incremental cost-effectiveness results based on probabilistic sensitivity analysis versus trial comparator SoC (with existing discount)

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
SoC	£24,358	1.27	-	-	-
Pembrolizumab combination	£72,745	2.95	£48,387	1.68	£28,852

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

The cost-effectiveness acceptability curve shows that, for the base case, there is an approximately 94% of chance of pembrolizumab combination being cost-effective when compared to SoC at the £50,000 per QALY threshold.

Figure 30: Scatterplot of PSA results (1,000 simulations) versus trial comparator SoC (with existing discount)

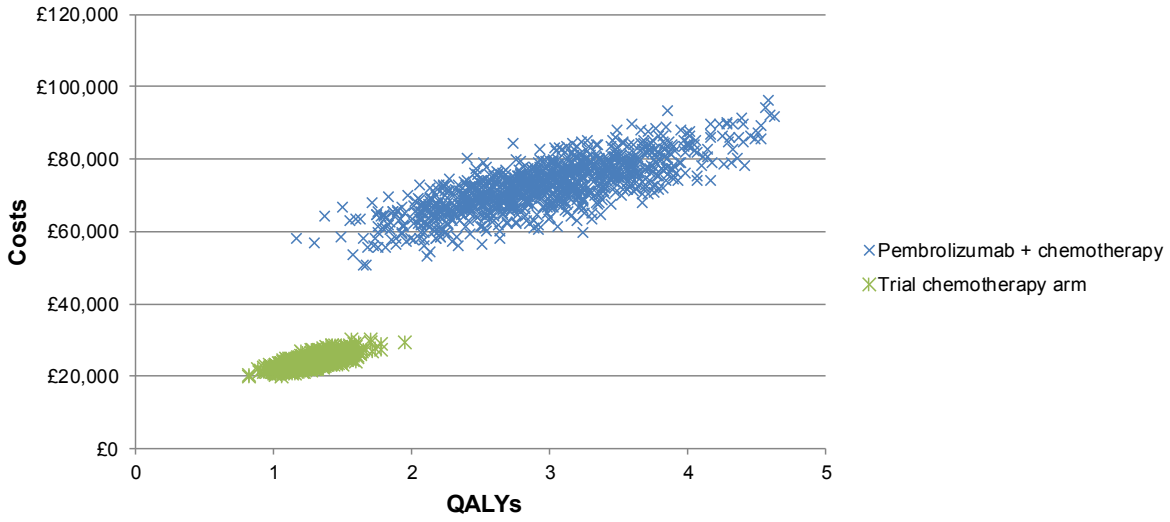
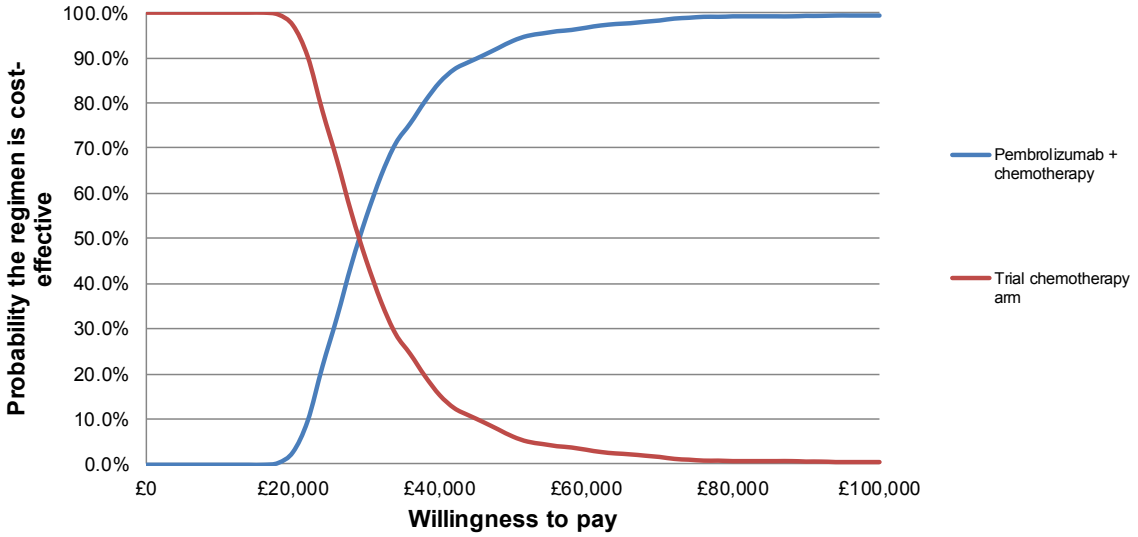


Figure 31: Cost-effectiveness acceptability curve versus trial comparator SoC (with existing discount)



B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted for the following key variables using the 5% and 95% confidence intervals for the variables except when it is indicated otherwise:

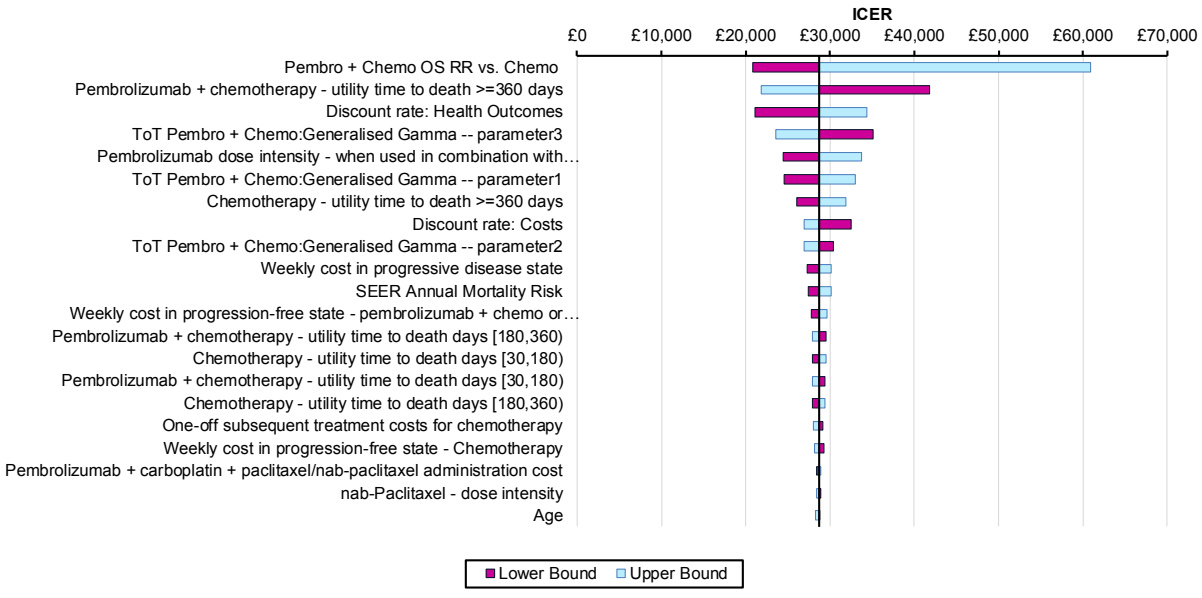
- Baseline characteristics (i.e. body surface area)
- Administration costs
- Resource utilisation
- Proportion of patients actually receiving the expected dose
- Subsequent treatment costs and mean duration of subsequent treatment
- Health-state related costs when on active treatment, when no active treatment and for terminal care
- Health-state utility values
- Proportion of patients experiencing AEs for pembrolizumab combination and SoC
- Costs of AEs

- Duration of AEs
- Parameters of the parametric curves fitted to PFS and ToT.
- RR of mortality from SEER
- RR of mortality pembro chemo vs SoC
- Discount rate (0% and 6%)

The results of the deterministic sensitivity analyses for pairwise comparisons of pembrolizumab combination vs. SoC are presented in Figure 32 below.

The inputs that most affect the ICERs are those related to modelling of OS (i.e. the pembrolizumab combination OS RR versus SoC), followed by the utility values for long-term survivors, assumptions around time on treatment and dose intensity considered to estimate the cost of pembrolizumab (see Figure 32).

Figure 32: Tornado diagram presenting the results of the deterministic sensitivity analysis for the 20 most sensible variables versus trial comparator SoC (with existing discount)



B.3.8.3 Scenario analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions:

- Parametric piecewise approach used to extrapolate OS, including:
    - A 19-week cut-off and exponential (scenario 1.a)
    - A 19-week cut-off and log logistic (scenario 1.b)
- Alternative cut-offs for the estimation of the parametric curve in the second phase of the piecewise approach used to extrapolate PFS, including:
    - A 16-week cut-off (scenario 2.a)
    - A 36-week cut-off (scenario 2.b)
- Impact of considering UK-based BSA (i.e. 1.79) [167], as suggested by the ERG for TA [94], instead of derived from KEYNOTE-407 (scenario 3).
- Assessing the impact of the half-cycle correction (scenario 4).
- Assuming the distribution of paclitaxel/nab-paclitaxel reflect UK market shares rather than KEYNOTE-407 distribution (scenario 5).
- Using progression-based utilities as an alternative approach to estimate QALYs based on KEYNOTE-407 (scenario 6).
- Using utilities derived per treatment arm instead of pooled utilities from KEYNOTE-407:
    - With the time to death approach (scenario 7.a)
    - With the progression-based approach (scenario 7.b)
- Removing the age-related disutilities (scenario 8).
- Assuming that the effect of treatment stops at 5 years (scenario 9), with pembrolizumab presenting a similar hazard to that of the SoC arm from that point onward.
- Using a generalised gamma curve for PFS at week 26 as the best statistical fitting – details in appendix L (scenario 10).

Table 91: Results from the scenario analyses versus trial comparator SoC (with existing discount)

		Pembrolizumab combination			SoC			Pembrolizumab combination vs SoC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Scenario 1.a	Parametric extrapolation OS cut-off – 19 weeks exponential	£58,483	1.87	1.36	£21,494	1.27	0.90	£36,989	0.46	£80,142
Scenario 1.b	Parametric extrapolation OS cut-off – 19 weeks Log-Logistic	£67,706	3.27	2.40	£26,653	2.14	1.55	£41,053	0.84	£48,706
Scenario 2.a	PFS cut-off – 16 weeks	£72,695	4.03	2.95	£24,417	1.76	1.27	£48,278	1.68	£28,672
Scenario 2.b	PFS cut-off – 36 weeks	£72,695	4.03	2.95	£24,417	1.76	1.27	£48,278	1.68	£28,672
Scenario 3	UK-specific BSA values (unadjusted by sex distribution)	£72,619	4.03	2.95	£24,340	1.76	1.27	£48,279	1.68	£28,673
Scenario 4	No half cycle correction	£72,694	4.03	2.96	£24,472	1.77	1.28	£48,222	1.68	£28,649
Scenario 5	Paclitaxel/nab-paclitaxel as for UK market shares	£70,320	4.03	2.95	£21,994	1.76	1.27	£48,326	1.68	£28,700
Scenario 6	Utilities – Progression based (pooled)	£72,695	4.03	2.70	£24,417	1.76	1.20	£48,278	1.49	£32,320
Scenario 7.a	Utilities – Time to death (per treatment arm)	£72,695	4.03	2.88	£24,417	1.76	1.30	£48,278	1.58	£30,580
Scenario 7.b	Utilities – Progression-based (per treatment arm)	£72,695	4.03	2.72	£24,417	1.76	1.19	£48,278	1.53	£31,567
Scenario 8	No age-related	£72,695	4.03	3.11	£24,417	1.76	1.31	£48,278	1.81	£26,737

		Pembrolizumab combination			SoC			Pembrolizumab combination vs SoC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
	disutilities									
Scenario 9	Assuming treatment effect stops at 5 years	£67,861	3.29	2.42	£24,417	1.76	1.27	£43,444	1.15	£37,730
Scenario 10	Parametric extrapolation PFS – 26 weeks GenGamma	£72,695	4.03	2.95	£24,417	1.76	1.27	£48,278	1.68	£28,672

B.3.8.4 Summary of sensitivity analyses results

The probability of pembrolizumab combination therapy being the most cost-effective treatment at a threshold of £50,000 per gained QALY is 94%.

One-way sensitivity analyses showed that the inputs that most affect the ICERs are those related to modelling of OS (i.e. the pembrolizumab combination OS RR versus SoC), followed by the utility values for long-term survivors, assumptions around time on treatment and dose intensity considered to estimate the cost of pembrolizumab.

Scenario analyses showed that the most sensitive scenarios relate to the utilisation of parametric extrapolation of OS versus the base case real world data extrapolation with the SA 1a and 1b ranging from £48,706 to £80,142. In addition to this, the scenario looking at treatment waning at 5 years also has a reasonable impact on the base case however still within the limits of cost-effectiveness using a WTP of £50,000. It should be noted that there is no evidence that the treatment effect stops with pembrolizumab treatment discontinuation.

The majority of scenario analyses produce ICERs below £50,000/QALY and therefore Pembrolizumab combination therefore should be considered a cost-effective strategy when realistic scenarios are considered

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B.3.9 Subgroup analysis

The results of the cost-effectiveness analyses on the subgroups of patients with the following different levels of PD-L1 expression versus trial comparator SoC are shown below:

- ≥50% TPS
  - Versus SoC
  - Versus pembrolizumab monotherapy as the expected SoC in this patient population since the recommendation of TA531 [94, 100]
- 1%≤TPS≤49%
- <1% TPS

The subgroup analysis has been conducted because it was pre-specified in the KEYNOTE-407 trial protocol [99] and analysis by PD-L1 expression was also pre-specified in the final scope [168]. Further detail on the statistical analysis and characteristics of the subgroups can be found in section B.2 and appendix E. Due to the smaller number of patients per subgroup, the results should be interpreted with caution versus the ITT. Base case distributions have been kept for subgroup analysis for consistency of results.

Patients whose tumours express PD-L1 with TPS≥50%

- OS as per the base case analysis – extrapolation with real world SEER data
- PFS cut-off point at 26 weeks (2-phase with Log Normal distribution in line with base case)
- ToT parametric approach (exponential distribution for both arms based on best statistical fit)

Table 92 Incremental cost-effectiveness results for the pembrolizumab combination vs. SoC for patients with TPS≥50% (with existing discount)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SoC	£24,401	1.79	1.29	-	-	-
Pembrolizumab combination	£69,030	3.90	2.86	£44,628	1.57	£28,380
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 93 Incremental cost-effectiveness results for the pembrolizumab combination vs. pembrolizumab monotherapy for patients with TPS≥50% (with existing discount)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab mono	£76,963	4.55	3.32	-	-	-
Pembrolizumab combination	£69,030	3.90	2.86	£7,934	0.46	£17,213
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

B.3.9.1 Patients whose tumours express PD-L1 with TPS1%≤TPS≤49%

- OS as per the base case analysis – extrapolation with real world SEER data
- PFS cut-off point at 26 weeks (2-phase with Log Normal distribution in line with base case)
- ToT parametric approach: GenGamma in line with base case).

Table 94 Incremental cost-effectiveness results for the pembrolizumab combination vs. SoC for patients with TPS 1%≥TPS≤49% (with existing discount)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SoC	£24,708	1.80	1.30	-	-	-
Pembrolizumab combination	£78,721	4.06	2.98	£54,013	1.68	£32,174
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Patients whose tumours express PD-L1 with TPS<1%

- OS as per the base case analysis – extrapolation with real world SEER data
- PFS cut-off point at 26 weeks (2-phase with Log Normal distribution in line with base case)
- ToT parametric approach: GenGamma in line with base case.

Table 95 Incremental cost-effectiveness results for the pembrolizumab combination vs. SoC for patients with TPS <1% (with existing discount)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
SoC	£25,443	1.66	1.19	-	-	-
Pembrolizumab combination	£70,000	3.96	2.90	£44,557	1.71	£26,012
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Clinical benefit

Comparing the model outcomes to clinical trial outcomes

The outcomes of the pembrolizumab combination therapy and the SoC arms of the KEYNOTE-407 trial have been compared to the outcomes from the model. For more details comparing the results generated from the model to the outcomes from the model please refer to Appendix J.

Expert validation

The model approach and inputs were validated by two external health economists (Dr. Chris Bojke, from the Centre for Health Economics, University of Leeds and Professor Alistair Grey from Oxford University). These individuals were selected as leading experts in health economic practice and methodology development in the UK. The model structure, selection of appropriate dataset, the survival analysis undertaken and assumption regarding extrapolation and the utility values used were all discussed.

Both experts were in agreement that the current model structure and key assumptions were valid and were mostly consistent with previous submissions in this indication. Regarding the assumption of treatment effect, they suggested that any assumptions in the model be provided with a clinical rationale. A five year treatment waning SA was included.

Regarding the crossover in the clinical trial and the adjustments applied, the experts agreed that it was reasonable not to perform crossover adjustment.

The HE experts agreed that the methods of assessing long term OS using SEER data could be valid and that the SA inclusion for OS using the parametric extrapolations suggested were also acceptable. The methods for extrapolation of PFS and ToT were also valid though they were not certain on the usefulness of a chow plot to determine cut points but it was also subsequently explained that the cumulative hazards plot is used in addition to this.

The experts noted that the KEYNOTE-407 trial collected good quality utility data and for a good number of patients and queried for additional information the compliance within the

trial. EQ-5D compliance data were included in the submission. They agreed with the base case using time-to-death utilities derived from pooling data from both treatment arms.

The experts agreed with the approach to identify AEs based on a 5% cut-off at the overall AE level, and with the way the AEs have been costed. They also agreed with the approach followed to costing, subsequent therapies and with inclusion of a SA included for UK SoC market share data.

The accuracy of the model development and programming was verified via internal quality control processes using an internal quality control checklist, available in Appendix M.

The OS projections, based on the April 2018 KEYNOTE-407 data cut, were validated with clinical experts. Given the changing treatment availability in the 2L, clinicians agreed on the plausibility of both the methods (utilising SEER data) and to estimate long term OS and the projections of the base case analyses presented in this submission with their estimations of SoC OS at 5 years.

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of pembrolizumab combination therapy for the treatment of patients with advanced squamous NSCLC who have not received prior systemic chemotherapy treatment in the UK. The economic evaluation reflects patients assessed in KEYNOTE-407 and is relevant to all groups of patients who could potentially benefit from use of the technology, as identified in the decision problem.

B.3.11.2 Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation was consistent with the advanced squamous NSCLC population eligible for pembrolizumab combination therapy as per its marketing authorisation. As mentioned previously (see section B.3.3), the KEYNOTE-407 trial, which assessed patients in line with the marketing authorisation, was used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially use pembrolizumab combination as first line therapy.

B.3.11.3 Generalisability of the analysis to the clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in KEYNOTE-407 and the de novo economic evaluation are reflective of patients with advanced NSCLC in the UK as validated by clinical experts. Some minor differences were identified between patients included in KEYNOTE-407 and those expected to be treated in clinical practice in England (mainly related to age and sex). These differences were considered to be minor and would not affect the benefit expected for patients treated in clinical practice.

- The economic model structure is consistent with other oncology models and previous NSCLC submissions to NICE.

- The resource utilitisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs and previous NICE submissions, incorporating the feedback provided by the ERGs in recent NICE appraisals. These cost inputs are considered most appropriate to model the cost-effectiveness of pembrolizumab combination.

- Extensive sensitivity analyses have been conducted in this updated evidence submission, considering alternative approaches to extrapolation and different data sources and scenarios related to the estimation of QALYs, costs and long term benefits, demonstrating that pembrolizumab combination is a cost-effective intervention in the majority of the analyses conducted.

- The OS projections of the model were validated against available UK sources and by clinical experts, to ensure the clinical plausibility of the model and its applicability to UK clinical practice.

B.3.11.4 Strengths and weaknesses of the evaluation

The cost-effectiveness analysis makes use of the best available evidence to inform the model, and this updated evidence submission makes use of the final data cut for KEYNOTE-407, which has a median follow up of 8.3 months.

- OS: Head-to-head data from the KEYNOTE-407 trial comparing pembrolizumab combination to SoC was used in the economic evaluation. The magnitude of benefit

observed in the SoC group was consistent with that previously observed with platinum-based combination regimens [39, 169].

- Crossover adjustments: Given that clinical practice in second line treatment for all PD-L1 expressors is different to that of non-expressors (i.e IO drugs are SoC for PD-L1 positive), it was not deemed appropriate not to conduct cross over adjustment for the base case ITT population.

- Estimation of utilities: Utility values were obtained from EQ-5D KEYNOTE-407 data. Four time categories were used for the time-to-death approach, which were consistent with values published by other utility studies identified from the systematic literature review.

- Treatment duration of pembrolizumab: The model assumed that patients will be treated for up to 2 years, as defined as part of the KEYNOTE-407 protocol and recommended by NICE for pembrolizumab in both first [94] and second line [94].

- Resource utilisation and unit costs used in the analysis are reflective of UK clinical practice and were mainly derived from recent NICE appraisals.

- There were limitations to the comparisons that can be drawn from the NMA versus other platinum chemotherapy options listed in the NICE scope due to paucity of data in the wholly squamous population. Further details can be found in section B.2.8 however as mentioned clinical experts and published data suggest that all of the options listed in the scope can be considered equal in this patient population.

Extensive sensitivity analyses were conducted to inform the uncertainty around the above limitations, which helped in understanding the key variables that have a major impact on the cost-effectiveness results and demonstrated that pembrolizumab combination therapy has the potential to offer a cost-effective option in the majority of the analyses considered.

Since the approaches taken for modelling are, in the main, conservative, the results presented here support the conclusion that, within the context of innovative therapies, pembrolizumab combination therapy is a cost-effective therapeutic option for the treatment of patients with previously untreated advanced squamous NSCLC.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]

Clarification questions

November 2018

File name	Version	Contains confidential information	Date
MSD response_ID1306 pembrolizumab clarification letter [REDACTED]	V1	Yes	05/12/18

MSD has provided an updated CE model in addition to the completed clarification letter which includes the following amends described in questions B8 and B30 part b and c:

- Updated the age-related disutility data
- Updates to life table

The base case result of these changes is presented below. It can be seen that these changes make very little difference to the overall results.

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Updated CS results	SoC	£24,413	1.76	1.27	-	-	
	Pembrolizumab combination	£72,617	4.01	2.94	2.25	1.68	£28,760
Original CS results	SoC	£24,417	1.76	1.27	-	-	-
	Pembrolizumab combination	£72,695	4.03	2.95	£48,278	1.68	£28,672

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

Section A: Clarification on effectiveness data

Literature searching

A1. In company submission (CS), appendices D1.1.1 Table 2 lines 1-2, search terms used for the condition Non-Small Cell Lung cancer (NSCLC) vary between the clinical effectiveness review and the economic/Health Related Quality of Life (HRQoL) review (CS appendices G1.1.1, Table 2 lines 1-5), reflecting a different way of conceptualising the disease between reviews. Searches carried out by us suggest that extra results would have been found for the clinical review had the disease terms from the economic review been used. Please comment on the reasons for the different approach to defining the disease area in the two reviews, and the possible implications in terms of missed studies.

The original clinical SLR was conducted in May 2016 to include an all histologies population (squamous and non-squamous). To be consistent across all subsequent SLR updates, the population search strategy terms have been unchanged and therefore do not contain the specific search terms for squamous cell histology found

in the economic review. The strategy to search for key terms in title and abstract as opposed to text word is to increase search specificity. We acknowledge that extra results may be found had the clinical review used disease terms from the economic review; however, we believe the disease terms used in the clinical review in combination with review of annual conference proceedings (ESMO, WCLC, AACR, and ASCO) to be sufficiently sensitive in capturing relevant trials for analyses.

A2. In CS appendices D1.1.1 Table 15, searches for the Systematic Literature Review (SLR) of clinical evidence were conducted in five phases. However, we are concerned that errors may have been made in some of the update searches. For example, the fourth update search of Medline concludes with a limit to entry dates in the range “ed=20160510-20170203” which would therefore mean it only covered articles added to the database up to early 2017 rather than June 2018 when it was run. Please explain the reasons for this approach or correct if appropriate.

A transcription error was made in the date limit line of the “Search term” column of Table 11-12 and 14-16. This error did not affect the searches themselves as demonstrated by number of “Hits” column, which is accurate and requires no amendment.

Line of 78 of Table 11 should be the following: limit 77 to dd=20171101-20180416

Line of 71 of Table 12 should be the following: limit 70 to ed=20171101-20180416

Line of 78 of Table 14 should be the following: limit 77 to dd=20180412-20180604

Line of 71 of Table 15 should be the following: limit 70 to ed=20180412-20180604

Line 7 of Table 16 should be the following: limit 6 to yr=2018-current

Study selection

A3. In CS section B2.2 page 29, please clarify the justification for including only primary data in the SLR and excluding systematic reviews/meta-analyses.

Systematic reviews and meta-analyses were excluded because any clinical trial identified in these studies will be identifiable in its preferred primary publication form.

A4. In CS appendices section D1.1.2.1 Table 18, some reasons for exclusion of trials from the Network Meta-Analysis (NMA) are not explicit. Please clarify the full reasons of exclusion for the 27 studies excluded for reason described as "other".

Specific exclusion sub-reasons are provided below. Clarification for studies excluded for reasons described as "other" can be found in section D.1.1.2 under subheading "Original search" where the paragraph states "27 [excluded] due to other reasons (e.g. publication type: letters, comments, protocols, etc.)".

Author	Year	Title	Journal	Reason for exclusion	Subreason
Original search					
[No authors listed]	2001	Study shows 2-year survival advantage for docetaxel	Expert review of anticancer therapy	Other	Publication type - review
Adamo et al	2006	Brain metastases in patients with non-small cell lung cancer: Focus on the role of chemotherapy	Annals of Oncology	Other	Publication type - review
Adams	2009	Maintenance pemetrexed therapy extends survival in nsclc	American Health and Drug Benefits	Other	Publication type - review
Adjei	2006	Clinical studies of pemetrexed and gemcitabine combinations	Annals of Oncology	Other	Publication type - review
Albain et al	2006	Pioneer: A phase iii randomized trial of paclitaxel poliglumex versus paclitaxel in chemotherapy-naive women with advanced-stage non-small-cell lung cancer and performance status of 2	Clinical Lung Cancer	Other	Publication type - protocol
Anonymous	1995	Vinorelbine for treatment of advanced non-small-cell lung cancer	Medical Letter on Drugs and Therapeutics	Other	Publication type - review
Anonymous	1996	Gemcitabine shows promise as combination agent in nsclc	Oncology (Williston Park, N.Y.)	Other	Publication type - review
Anonymous	2001	Docetaxel combination produces 2-year survival advantage in nsclc patients	Oncology (Williston Park, N.Y.)	Other	Publication type - review

Anonymous	2009	Maintenance therapy with pemetrexed improves overall survival in advanced nsclc	Oncology	Other	Publication type - review
Anonymous	2012	First-line erlotinib inferior to chemo in advanced lung cancer	Oncology (Williston Park)	Other	Publication type - review
Anonymous	2014	Erlotinib plus bevacizumab is effective in egfr-mutant nsclc	Cancer discovery	Other	Publication type - review
Bepler	2007	Phase ii pharmacogenomics-based adjuvant therapy trial in patients with non-small-cell lung cancer: Southwest oncology group trial 0720	Clinical Lung Cancer	Other	Publication type - protocol
Bianco et al	2006	Combination of biological therapies in non-small cell lung cancer	Annals of Oncology	Other	Publication type - review
Bogart and Govindan	2006	A randomized phase ii study of radiation therapy, pemetrexed, and carboplatin with or without cetuximab in stage iii non-small-cell lung cancer	Clinical Lung Cancer	Other	Publication type - protocol
Chiou and Burotto	2015	Pseudoprogression and immune-related response in solid tumors	Journal of Clinical Oncology	Other	Publication type - review
Clerici et al	1995	Non small cell lung cancer treatment with vinorelbine monochemotherapy: A phase ii study	Anticancer Research	Other	Not found
Crino	2002	Combined platinum containing treatment in nsclc	Lung Cancer	Other	Publication type - review
Favaretto	2006	Non-platinum combination of gemcitabine in nsclc	Annals of Oncology	Other	Publication type - review
Fisher	2002	Docetaxel plus cisplatin combinations in advanced non-small-cell lung cancer	Clinical Lung Cancer	Other	Publication type - review
Hightower et al	2003	Erlotinib (osi-774, tarcevatm), a selective epidermal growth factor receptor tyrosine kinase inhibitor, in combination with chemotherapy for	Clinical Lung Cancer	Other	Publication type - review

		advanced non-small-cell lung cancer			
Kosmidis et al	1997	Paclitaxel (175 mg/m2) plus carboplatin versus paclitaxel (225 mg/m2) plus carboplatin in non-small cell lung cancer: A randomized study	Seminars in oncology	Other	Not found
Kosmidis et al	2000	Combination chemotherapy with paclitaxel plus carboplatin versus paclitaxel plus gemcitabine in inoperable non-small cell lung cancer: A phase iii randomized study. Preliminary results	Seminars in Oncology	Other	Not found
Li et al	2011	A randomized study of gemcitabine plus oxaliplatin versus gemcitabine plus cisplatin as the 1st line chemotherapy for advanced non-small cell lung cancer in elderly patients	Chinese Journal of Lung Cancer	Other	Not English
Maneechawakajorn and Suksuperm	2014	Quality of life in advanced non-small cell lung cancer receiving chemotherapy of platinum combination in old versus new standard chemotherapy regimen	Journal of the Medical Association of Thailand	Other	Not found
Maung et al	2002	Ly900003 (affinitactm), an antisense inhibitor of protein kinase c-alpha, in non-small-cell lung cancer	Clinical Lung Cancer	Other	Publication type - protocol
Yaqub	2015	Nivolumab for squamous-cell non-small-cell lung cancer	The Lancet	Other	Publication type - editorial
Yu and Lu	2009	Perioperative chemotherapy of stage iii n2 non-small cell lung cancer	Chinese-German Journal of Clinical Oncology	Other	Publication type - review
Second Update					
Addeo	2017	A new frontier for targeted therapy in nsclc: Clinical efficacy of pembrolizumab in the inhibition of	Expert review of anticancer therapy	Other	Publication type - review

		programmed cell death 1 (pd-1)			
Anonymous	2016	Nivolumab may work as first-line nsclc therapy	Cancer Discovery	Other	Publication type - review

A5. In CS section B.2.8 page 83, please clarify why KEYNOTE-024 and KEYNOTE-042 were excluded from the NMA if patients with any PD-L1 status are included in the model?

Any PD-L1 status in the NMA refers to patients randomized to pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin or carboplatin + paclitaxel/nab-paclitaxel in KEYNOTE-407, which enrolled patients regardless of their PD-L1 expression status. All NMA networks were constructed to only include trials that enrolled patients regardless of their PD-L1 status. Both KEYNOTE-024 and KEYNOTE-042 enrolled patients with only a PD-L1 strong-expressing tumour (KEYNOTE-024) or a PD-L1 positive tumour (KEYNOTE-042), therefore, these two trials were not included in networks of evidence as explained in section B.2.9.1. PD-L1 expression is a known treatment effect modifier, as such, we determined networks of evidence should not include trials that enrolled only PD-L1 expressing patients.

A separate ITC was conducted to provide the comparative efficacy of pembrolizumab combination versus pembrolizumab monotherapy in the high PD-L1 expressers as detailed in Section B.2.9.2; results of this ITC fed into the model.

Adverse events

A6. Priority question: In CS appendices section F page 185, it states “No additional safety data in the population of interest are available.” Please provide summary data or perform NMAs of (a) treatment-related grade 3/4 Adverse Events (AEs) and (b) discontinuation due to AEs for pembrolizumab combination versus pembrolizumab monotherapy versus chemotherapy comparators using KEYNOTE-407, KEYNOTE-024 and patients with squamous disease in KEYNOTE-042 (relevant MSD trials where AE data are recorded and reported consistently). Please stratify by PD-L1 status if possible.

Data on Grade 3-5 AEs from KEYNOTE-407 are provided in Section B.2.10.3, Table 49 of our submission. Similarly, discontinuations due to AEs are provided in Table 46.

A summary of the AE profile observed in both treatment groups for KEYNOTE-024 ASaT subpopulation with squamous histology is displayed in the table below.

Adverse Event Summary KN-024
(ASaT Population with Squamous Histology)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	[redacted]	[redacted]	[redacted]	[redacted]
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related† adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued‡ due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued due to a serious drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.
AEs were followed 30 days after last dose of study treatment.
SAE is monitored until 90 days after last dose.
(Database Cutoff Date: 10JUL2017).

Source: [P024V02MK3475: analysis-adsl; adae] [P024V02MK3475: tabulations-aeplus]

A summary of the AE profile observed in both treatment groups for KEYNOTE-042 ASaT subpopulation with squamous histology, ASaT subpopulation with squamous histology and TPS 1-49%, and ASaT subpopulation with squamous histology and TPS ≥50% are displayed in the tables below.

Adverse Event Summary KN-042
(ASaT Population with Squamous Histology)

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	[redacted]	[redacted]	[redacted]	[redacted]
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related† adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]

† Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 4.03.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adae]

Adverse Event Summary KN-042
(ASaT Population with Squamous Histology and TPS=1-49%)

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	[redacted]	[redacted]	[redacted]	[redacted]
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related† adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]

† Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 4.03.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adae]

Adverse Event Summary KN-042
(ASaT Population with Squamous Histology and TPS>=50%)

	Pembrolizumab		Chemotherapy	
	n	(%)	n	(%)
Subjects in population	[redacted]	[redacted]	[redacted]	[redacted]
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related† adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]

† Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 4.03.

MedDRA preferred terms "Neoplasm Progression" and "Malignant Neoplasm Progression" not related to the drug are excluded.

AEs were followed 30 days after last dose of study treatment.

SAE is monitored until 90 days after last dose.

Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adae]

A7. Priority question: In CS section B.2.10.3 page 115, it states “Non-serious adverse events up to 30 days of last dose and serious adverse events (SAEs) up to 90 days of last dose are included.” The KETRUDA website (https://www.keytruda.com/important-safety-information/) states “KEYTRUDA can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. These problems may happen any time during treatment or even after your treatment has ended.” Please provide a summary of AEs and SAEs that occurred after 90 days in the KEYNOTE-407 trial to present.

At present, we can only access the locked KN407 database with cut-off [redacted] and retrieve information recorded up to this cut-off. In the locked database, there is [redacted] in the combination arm who has [redacted] non-serious AEs that occurred +90 days treatment discontinuation. In the control arm there are several incidences.

A8. Priority question: In CS section B.2.3 page 38, it states “There were no prohibited therapies during the Post-Treatment Follow-Up Phase.” Please clarify what proportion (if any) of patients in the pembrolizumab + chemotherapy arm of KEYNOTE-407 received a second immunotherapy, such as nivolumab, post-discontinuation, either during or after the trial.

Details of subsequent antineoplastic therapies received by patients following discontinuation of initial study treatment in both the pembrolizumab chemotherapy and control arms of KEYNOTE-407 are presented in the appendices document Appendix D1.3, Table 79. As the table shows, [redacted] patients in the pembrolizumab combination arm ([redacted] nivolumab; [redacted] pembrolizumab) and [redacted] patients in the control arm ([redacted] nivolumab, [redacted] pembrolizumab) received subsequent immunotherapy treatment.

Statistical analyses

A9. In CS section B.2.4 page 40, please clarify the power to detect statistically significant differences in Overall Survival (OS) and Progression Free Survival (PFS) at interim analysis 2.

Details of the statistical analyses, including multiplicity, sample size and power are presented in Section B.2.4 Table 8 of our submission. As detailed below, for PFS,

with [redacted] events at IA2, the study has ~ [redacted] power for detecting a HR of [redacted] at initially assigned [redacted] (one-sided) significance level, ~ [redacted] power for detecting a HR of [redacted] at [redacted] (one-sided) significance level, ~ [redacted]power for detecting a HR of [redacted] at [redacted] (one -sided) significance level, and ~ [redacted] power for detecting a HR of [redacted] at [redacted] (one-sided) significance level. For OS, with [redacted] deaths, the study has ~ [redacted] power for detecting a hazard ratio (HR) of [redacted] at [redacted] (one-sided) significance level, ~ [redacted] power for detecting a HR of [redacted] at [redacted] (one-sided significance level, and ~ [redacted] power for detecting a HR of [redacted] at [redacted] (one-sided) significance level.

Efficacy Boundaries and Properties for Progression-free Survival Analyses

Analysis	Value	α=0.01	α=0.015	α=0.02	α=0.025
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Percentage of expected number of events at final analysis required at interim analysis
§ p (1-sided) is the nominal alpha for testing.
% HR at bound is the approximate HR required to reach an efficacy bound
† P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis
# P(Cross if HR=0.7) is the cumulative probability of crossing a bound under the alternative hypothesis

Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	Value	α =0.01	α =0.02	α =0.025
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Percentage of expected number of events at final analysis required at interim analysis
§ p (1-sided) is the nominal alpha for testing.
% HR at bound is the approximate HR required to reach an efficacy bound
† P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis
# P(Cross if HR=0.7) is the cumulative probability of crossing a bound under the alternative hypothesis

A10. In CS section B2.8 page 84, please clarify whether the reported point estimates for the hazard ratios from NMAs (Table 33-38 and Table 40-41) are means or medians.

We can confirm the reported point estimates for the hazard ratios from the NMAs are medians.

A11. In CS section B2.8 page 80, for NMA 2 (unselected for histology) please clarify whether excluding the studies which did not report the proportion of non-squamous patients would result in significantly different estimate for the treatment effects when comparing to the results from the NMA with missing proportion of non-squamous patients imputed.

In NMA 2 for overall survival (unselected for histology), only one trial (SWOG 9509) did not report the proportion of squamous patients. Because other trials inform the same connection, it is unlikely results would differ significantly if the proportion of squamous patients had not been imputed for this arm. NMA 2 for progression-free

survival did not contain any imputed proportions of non-squamous patients as all trials reported the proportion of squamous patients.

A12. In CS section B2.9 page 80, please clarify why fractional polynomial models with negative power were not used?

In this analysis, powers were set to either 0 or 1. Negative powers, as well as powers other than 0 or 1 were not used as they are associated with over-fitting the Kaplan-Meier data which leads to unstable estimates of the HRs versus the reference over time. The flexibility of using powers set to 0 or 1 was considered sufficient in providing monotonically increasing or decreasing time-varying HR curves over time versus the reference treatment, thus providing stable HR estimates over time.

A13. Please clarify what was the burn-in period and the number of iterations used for making inferences for each NMA analysis (first mentioned – CS Section B.2.9.1 page 80), and how the convergence of the chains was checked.

NMA 1 and NMA 2 constant HR used 50,000 iterations, burn-in period was 25,000. Convergence of chains was checked by inspecting Gelman plots.

A14. Priority question: Please provide the BUGS code used for synthesising both constant hazard ratios (first mentioned – CS section B.2.9.1 table 33 page 84) and time-varying hazard ratios (first mentioned – CS section B.2.9.1 page 83), including the meta-regression model.

Please refer to Metaregression BUGS code.docx (provided separately)

A15. In CS appendices section D1.2.3.1, please provide the model equation for model 9 and model 10.

Model 9:

$$\ln(h_{jkt}) = \beta_{0jk} + \beta_{1jk} t^{p} \qquad \text{with } t^{0} = \log(t) \tag{9}$$

$$\begin{pmatrix} \beta_{0jk} \\ \beta_{1jk} \end{pmatrix} = \begin{cases} \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \end{pmatrix} & if\ k = b \\ \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \end{pmatrix} + \begin{pmatrix} \delta_{0jbk} \\ d_{1Ak} - d_{1Ab} \end{pmatrix} & if\ k \succ b \end{cases}$$

$$\delta_{0jbk} \sim N(d_{0Ak} - d_{0Ab}, \sigma^{2})$$

Model 10:

$$\ln\left(h_{jkt}\right)=\beta_{0jk}+\beta_{1jk}t^{p} \qquad \text{with } t^{0}=\log(t), \quad p\in\{0,1\} \tag{10}$$

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\end{pmatrix}=\begin{cases}\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix} & if\ k=b, b\in\{A,B,C\}\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix}+\begin{pmatrix}d_{0Ak}-d_{0Ab}+\beta X_{j}\\ d_{1Ak}-d_{1Ab}\end{pmatrix} & if\ k\succ b \text{ and } b=A\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix}+\begin{pmatrix}d_{0Ak}-d_{0Ab}\\ d_{1Ak}-d_{1Ab}\end{pmatrix} & if\ k\succ b \text{ and } b\neq A\end{cases}$$

A16. Please provide the estimated between-study standard deviation when a random effects model was used (first mentioned – CS section B.2.9.1 page 87).

NMA 2 OS standard deviation can be found in Table 36 last row (SD = 0.08)

NMA 2 PFS standard deviation can be found in Table 38 last row (SD = 0.11)

A17. Please provide the estimated coefficient for the covariate when a meta-regression was used (first mentioned – CS section B.2.9.1 page 91).

The covariate used for meta-regression in NMA 2 for both OS and PFS was:

$$proportion\ nonsquamous = 1 - proportion\ squamous$$

Covariate vector used for NMA 2, OS:

Trial Name	Proportion Non-squamous
Chang 2008	0.712329
Chen 2004	0.814286
Chen 2007	0.787234
Comella 2000	0.511111
Douillard 2005	0.673820
EORTC 08975	0.779167
Ferry 2017	0.664710
Gebbia 2003	0.478417
GFPC 99-01	0.570000
Helbekkmo 2007	0.745370
Kawahara 2013	0.744444
KEYNOTE-407	0.000000
Martoni 2005	0.713235
Mazzanti 2003	0.716667
Rosell 2002	0.624595
Saad 2017	0.000000
SWOG 9509	0.643588
Treat 2010	0.822026
Zatloukal 2003	0.488636
TAX 326	0.665025

FACS	0.795872
Scagliotti 2002	0.691928
ECOG 1594	0.000000

Covariate vector used for NMA 2, PFS:

Trial Name	Proportion Non-squamous
Chen 2004	0.814286
Chen 2007	0.787234
CTONG 1002	0.000000
EORTC 08975	0.779167
Gebbia 2003	0.478417
GFPC 99-01	0.570000
GLOB 3	0.661417
Kawahara 2013	0.744444
KEYNOTE-407	0.000000
Martoni 2005	0.713235
Mazzanti 2003	0.716667
Rosell 2002	0.624595
Saad 2017	0.000000
Treat 2010	0.822026
Zatloukal 2003	0.488636
FACS	0.795872
Scagliotti 2002	0.691928
ECOG 1594	0.000000

A18. Priority question: In CS appendices section D1.2.3.2 page 150, please clarify how the Inverse Probability of Treatment Weighting (IPTW) method was performed among the four treatment arms?

Details of how the IPTW method was performed are presented in Section D1.2.3.2 of our submission under the sub-heading ‘Methods’. In addition, under the sub-heading ‘Presentation of results’ details of the weight calculated for each subject (Table 73), subject characteristics before weighting (Table 74) and after weighting (Table 75) and the maximum standardised difference among the pairwise treatment arms (Table 76) were also presented.

A19. Priority question: In CS appendices section D1.2.3.2 page 150, please provide the distribution of propensity scores for each treatment arm to assess

overlap, the standardised differences for each covariate before and after weighting, and the ratio of the variance for each covariate before and after weighting.

The maximum of standardized differences among all pairwise imbalance assessments between the 4 treatment arms in subjects with strong PD-L1 (TPS≥50%) were presented in Section D1.2.3.2, Table 76 of our submission. The table below reports the maximum of ratios of the variances among all pairwise treatments of the 4 arms. These two statistics are shown before and after weighting for all the selected effect modifiers: ECOG PS (0 vs. 1), smoking status (never vs. former/current), gender (female vs. male), baseline tumor size and age.

The maximum variance ratios among all the pairwise treatment arms (ITT Population TPS≥50%)

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

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

The figure below displays the distribution of propensity scores for each of the 4 treatment arms in subjects with strong PD-L1 (TPS≥50%).

Distribution of Propensity Score for each treatment arm
(ITT Population, TPS ≥ 50%)

A20. Priority question: Please provide the patient baseline characteristics for squamous and PD-L1 strong expression (Tumor proportion score [TPS] ≥50%) patients from KEYNOTE-024 (first mentioned – CS section B.2.2 page 29).

Subject baseline characteristics for KEYNOTE-024 ITT subpopulation with squamous histology is displayed in **Error! Reference source not found.**the table below:

Subject Characteristics
(ITT Population with Squamous Histology)

	Pembrolizumab		SOC	
	n	(%)	n	(%)
Subjects in population	[redacted]		[redacted]	
Gender				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Age (Years)				
< 65	[redacted]	[redacted]	[redacted]	[redacted]
>= 65	[redacted]	[redacted]	[redacted]	[redacted]

Mean	[redacted]		[redacted]	
SD	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Range	[redacted]		[redacted]	
Race				
Asian	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity				
Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]
ECOG				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
Cancer Stage at Screening				
IIIB	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region of Enrolling Site				
Non-East Asia	[redacted]	[redacted]	[redacted]	[redacted]
East Asia	[redacted]	[redacted]	[redacted]	[redacted]
Histology				
SQUAMOUS CELL CARCINOMA	[redacted]	[redacted]	[redacted]	[redacted]
POORLY DIFFERENTIATED SQUAMOUS CELL CARCINOMA	[redacted]	[redacted]	[redacted]	[redacted]
Smoking Status				
Current	[redacted]	[redacted]	[redacted]	[redacted]
Former	[redacted]	[redacted]	[redacted]	[redacted]
Never	[redacted]	[redacted]	[redacted]	[redacted]
Brain Metastasis Status at Baseline				
Y	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Tumor Size (mm)				
Subjects with data	[redacted]		[redacted]	
Mean	[redacted]		[redacted]	
SD	[redacted]		[redacted]	
Median	[redacted]		[redacted]	

Range	[redacted]		[redacted]	
Baseline Weight (kg)				
Subjects with data	[redacted]		[redacted]	
Mean	[redacted]		[redacted]	
SD	[redacted]		[redacted]	
Median	[redacted]		[redacted]	
Range	[redacted]		[redacted]	
Prior Adjuvant Therapy				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Prior Neo-adjuvant Therapy				
No	[redacted]	[redacted]	[redacted]	[redacted]
(Database Cutoff Date: 10JUL2017).				

Source: [P024V02MK3475: analysis-adsl]

A21. Priority question: Please include squamous and PD-L1 strong expression (TPS ≥50%) patients from KEYNOTE-024 (first mentioned – CS section B.2.2 page 29) in the analysis for pembrolizumab combination versus. pembrolizumab monotherapy.

As documented in the submission, no data were included from KEYNOTE-024 as the population of patients with squamous histology who received paclitaxel + carboplatin chemotherapy was very small (n=[redacted] in each treatment arm).

It is considered that the addition of these [redacted] patients from KEYNOTE 024 will not have a major impact on the results of the indirect treatment comparison (ITC) of pembrolizumab combination versus pembrolizumab monotherapy.

For OS, the ITC outcome based on KN407 versus KN042 gives an HR=[redacted] [[redacted]; [redacted]], p=[redacted]; thus, no evidence of a difference between the pembrolizumab combination therapy and pembrolizumab monotherapy.

This comparison is based on:

- Comparison of pembrolizumab combination versus chemotherapy involving [redacted] patients with HR=[redacted]
- Comparison of pembrolizumab monotherapy versus chemotherapy involving [redacted] patients with HR=[redacted]

Adding the [redacted] patients from KN024 into this second comparison gives [redacted] patients for the comparison of pembrolizumab monotherapy versus chemotherapy. With [redacted] % more data for this comparison, it is expected that there won't be a major change to the observed HR for the comparison of pembrolizumab monotherapy versus chemotherapy.

Various scenarios can be considered:

- Adding [redacted] patients from KN024 to the comparison of pembrolizumab monotherapy versus chemotherapy changes the observed HR=[redacted] to HR=[redacted]. This will lead to a HR=[redacted] for the comparison between pembrolizumab combination therapy and pembrolizumab monotherapy. Hence, the conclusion of no evidence of a difference between the pembrolizumab combination therapy and pembrolizumab monotherapy is still valid.
- Adding [redacted] patients from KN024 to the comparison of pembrolizumab monotherapy versus chemotherapy changes the observed HR=[redacted] to HR=[redacted]. This will lead to a HR=[redacted] for the comparison between pembrolizumab combination therapy and pembrolizumab monotherapy. Hence, the conclusion of no evidence of a difference between the pembrolizumab combination therapy and pembrolizumab monotherapy is still valid.
- Among the [redacted] patients from KEYNOTE 024, [redacted] patients died; [redacted] in the pembrolizumab monotherapy arm and [redacted] in the chemotherapy arm leading to a relative risk (RR)=[redacted]. A rough and scientifically incorrect approximation (weighted average) would lead to a HR around [redacted] for the comparison of pembrolizumab monotherapy versus chemotherapy and thus a HR=[redacted] for the comparison between pembrolizumab combination therapy and pembrolizumab monotherapy. Hence, the conclusion of no evidence of a difference between the pembrolizumab combination therapy and pembrolizumab monotherapy is still valid.

For PFS, the ITC outcome based on KN407 versus KN042 gives an [redacted] [[redacted]:[redacted]], p=[redacted]; thus, a numerical benefit of the pembrolizumab combination therapy over pembrolizumab monotherapy.

This comparison is based on:

- Comparison of pembrolizumab combination versus chemotherapy involving [redacted] patients à HR=[redacted]

- Comparison of pembrolizumab monotherapy versus chemotherapy involving [redacted] patients à HR=[redacted]

Adding the [redacted] patients from KN024 into this second comparison gives [redacted] patients for the comparison of pembrolizumab monotherapy versus chemotherapy. With [redacted] % more data for this comparison, it is expected that there won't be a major change to the observed HR for the comparison of pembrolizumab monotherapy versus chemotherapy.

Various scenarios can be considered:

- Adding [redacted] patients from KN024 to the comparison of pembrolizumab monotherapy versus chemotherapy changes the observed HR=[redacted] to HR=[redacted]. This will lead to a HR=0.63 for the comparison between pembrolizumab combination therapy and pembrolizumab monotherapy. Hence, the conclusion of a numerical benefit of the pembrolizumab combination therapy over pembrolizumab monotherapy. is still valid.
- Adding [redacted] patients from KN024 to the comparison of pembrolizumab monotherapy versus chemotherapy changes the observed HR=[redacted] to HR=[redacted]. This will lead to a HR=[redacted] for the comparison between pembrolizumab combination therapy and pembrolizumab monotherapy. Hence, the conclusion of a (numerical) benefit of the pembrolizumab combination therapy over pembrolizumab monotherapy. Whether the difference between the 2 regimens would be significant or not is not of primary interest. The main purpose of the ITC is to estimate the treatment difference rather than formal testing. As stated in the submission, a head to head clinical trial would be required for a definitive analysis comparing pembrolizumab + chemotherapy and pembrolizumab monotherapy.
- Among the [redacted] patients from KEYNOTE 024, [redacted] patients had a PFS event; [redacted] in the pembrolizumab monotherapy arm and [redacted] in the chemotherapy arm leading to a relative risk (RR)=[redacted]. A rough and scientifically incorrect approximation (weighted average) would lead to a HR around [redacted] for the comparison of pembrolizumab monotherapy versus chemotherapy and thus a HR=[redacted] for the comparison between pembrolizumab combination therapy and pembrolizumab monotherapy. Hence, the conclusion of a (numerical) benefit of the pembrolizumab combination therapy over pembrolizumab monotherapy is still valid.

A22. Priority question: Please provide the hazard ratio and 95% confidence interval of intervention versus control treatment and perform an NMA for the overall survival and progression-free survival for the following trial populations (first mentioned – CS section B.1.1 table 1 page 15 and section B.2.2 page 29)

- KEYNOTE-407 squamous and PD-L1 strong expression (TPS ≥50%) patients
- KEYNOTE-042 squamous and PD-L1 strong expression (TPS ≥50%) patients
- KEYNOTE-024 squamous and PD-L1 strong expression (TPS ≥50%) patients

Results of the OS and PFS analysis for KEYNOTE-407 PD-L1 strong expression patients were presented in Section B.2.6.2 and B.2.6.3 of our submission. See below for the data for KN024 and KN042 trials.

The results of the OS analysis and PFS analysis for KEYNOTE-024 ITT subpopulation with squamous histology are described in the tables below.

Analysis of Overall Survival KN-024
Squamous Histology
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)	OS Rate at Month 24 in %† (95% CI)	Pembrolizumab vs. SOC	
								Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab 200mg Q3W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia) and ECOG PS (0 vs. 1).
‡‡ Two-sided p-value based on log-rank test.
NR: Not Reached
(Database Cutoff Date: 10JUL2017)

Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule) KN-024
Squamous Histology
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)	PFS Rate at Month 24 in %† (95% CI)	Pembrolizumab vs. SOC	
								Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab 200mg Q3W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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

‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia) and ECOG PS (0 vs. 1).

‡‡ Two-sided p-value based on log-rank test.

NR: Not Reached

(Database Cutoff Date: 10JUL2017)

The results of the OS analysis and PFS analysis for KEYNOTE-042 ITT subpopulation with squamous histology and TPS ≥50% are described in the following tables.

Analysis of Overall Survival
(ITT Population with Squamous Histology and TPS>=50%)

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)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia) and ECOG PS (0 vs. 1).

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

Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adtte]

Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Primary Censoring Rule)
(ITT Population with Squamous Histology and TPS>=50%)

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)	Pembrolizumab vs. Chemotherapy	
							Hazard Ratio‡ (95% CI)‡	p-Value‡‡
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

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

‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (East Asia vs. non-East Asia) and ECOG PS (0 vs. 1).

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

Database Cutoff Date: 26FEB2018

Source: [P042V01MK3475: adam-adsl; adtte]

Section B: Clarification on cost-effectiveness data

B1. In CS appendices G1 page 187 it states that bibliographies of relevant SLRs, meta-analyses and Health Technology Assessment (HTA) submissions were manually checked for relevant missed studies. Was any forward tracking of citations undertaken for included papers?

In line with standard practices as searches of bibliographies and online databases, in addition to the standard electronic databases, congresses and HTA websites were conducted, forward tracking of ultimately included papers was not performed due to the low likelihood that any relevant papers had been missed by the search strategy undertaken.

B2. In CS appendices G Table 1 pages 187-190, please acknowledge sources for the study type search filters used for the three reviews and the geographic (UK) filter applied to the cost/resource use results and provide citations to published validation studies where available.

Terms for economic studies are distributed between the "economic evaluations" (lines 9−15) and "cost/resource use studies" (lines 34−63) term groups in the Table below. The search terms are based on the "economic studies" search filter developed by the Scottish Intercollegiate Guidelines Network [1] (SIGN).

Terms for health state utilities (lines 16−32) are aligned with recommendations developed by the School of Health and Related Research (ScHARR) at the University of Sheffield [2] and the York Health Economics Consortium [3] (YHEC).

The UK search filter used in the search strategy (lines 65–72) was developed by NICE [4]. As noted in the CS in the legend of the Table below (in appendix G on page 189), this filter was adapted slightly to include Ireland due to the potential for a future submission in Ireland. The geographic filter has been applied to the "cost/resource use studies" only (line 73), in line with the NICE reference case and the perspective of the economic model.

Study type and geographic search filters used for the systematic literature review (Table 1 of appendix G in the CS)

Term group	#	Searches
Non-small cell lung cancer	1	NSCLC.tw.
	2	exp Carcinoma, non-small-cell lung/
	3	exp Lung/ and (exp Neoplasms/ or exp Neoplasms, squamous cell/ or exp Carcinoma, squamous cell/)
	4	((lung or pulmon$ or bronchial) adj2 (carcinoma$ or cancer$ or tumo?r$ or neoplasm$ or squamous cell or squamouscell)).tw.
	5	(nonsmall cell or non small cell or non smallcell).tw.
	6	3 or 4
	7	6 and 5
	8	or/1-2,7
Economic evaluations and health state utilities	9	Cost-benefit analysis/
	10	"Costs and cost analysis"/
	11	Quality-adjusted life years/
	12	Value of life/
	13	Economics/
	14	(cost$ adj (effective$ or utilit$ or consequence$ or benefit$ or minimi$)).tw.
	15	(economic evaluation$ or economic analysis or QALY$ or DALY$ or quality adjusted or adjusted life year$ or disability adjusted life or qald$ or qale$ or qtime$ or life year$ gained or ICER).ti,ab,kf.
	16	(health utilit$ or health state$1 or illness state$1 or HSUV or HSUVs or health state$ value$ or health state$ preference$ or utility assessment$ or utility measure$ or preference based or utility based).ti,ab,kf.

Term group	#	Searches
	17	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf.
	18	(multiattribute$ or multi attribute$).ti,ab,kf.
	19	utility.ab. /freq=2
	20	(utilities or disutilit$).ti,ab,kf.
	21	(health$1 year$1 equivalent$1 or hye or hyes).ti,ab,kf.
	22	(hui or hui1 or hui2 or hui3 or rosser).ti,ab,kf.
	23	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d or eq-sdq or eqsdq).ti,ab,kf.
	24	(short form$ or shortform$).ti,ab,kf.
	25	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.
	26	(sf6 or sf 6 or sf6d or sf 6d or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).ti,ab,kf.
	27	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf.
	28	(sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf.
	29	(sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf.
	30	(15D or 15-D or 15 dimension).ti,ab,kf.
	31	(standard gamble$ or sg).ti,ab,kf.
	32	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.
	33	or/9-32
Cost/resource use studies	34	Cost allocation/
	35	Cost control/
	36	Cost savings/

Term group	#	Searches
	37	Cost of illness/
	38	Cost sharing/
	39	"Deductibles and coinsurance"/
	40	Medical savings accounts/
	41	Health care costs/
	42	Direct service costs/
	43	Drug costs/
	44	Employer health costs/
	45	Hospital costs/
	46	Health expenditures/
	47	Capital expenditures/
	48	exp economics, Hospital/
	49	exp economics, Medical/
	50	Economics, nursing/
	51	Economics, pharmaceutical/
	52	"Fees and charges"/
	53	exp Budgets/
	54	Financial management/
	55	(low adj cost).mp.
	56	(high adj cost).mp.
	57	(health?care adj cost$).mp.
	58	(fiscal or funding or financial or finance).tw.

Term group	#	Searches
	59	(cost adj estimate$).mp.
	60	(cost adj variable$).mp.
	61	(unit adj cost$).mp.
	62	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.
	63	((resource$ or healthcare$ or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).tw.
	64	or/34-63
Geographic filters	65	United Kingdom/ or Ireland/
	66	(national health service$ or nhs$).ti,ab,in.
	67	(english not ((published or publication$ or translat$ or written or language$ or speak$ or literature or citation$) adj5 english)).ti,ab.
	68	(gb or "g.b." or britain$ or (british$ not british columbia) or uk or "u.k." or united kingdom$ or (england$ not new england) or Ireland$ or irish$ or scotland$ or scottish$ or ((wales or south wales) not new south wales) or welsh$).ti,ab,jw,in.
	69	(Aberdeen or Armagh or Bangor or Bath or Belfast or Birmingham or Bradford or Brighton or Bristol or Cambridge or Canterbury or Cardiff or Carlisle or Chelmsford or Chester or Chichester or Cork or Coventry or Derby or Derry or Dundee or Dublin or Durham or Edinburgh or Ely or Exeter or Galway or Glasgow or Gloucester or Hereford or Inverness or Kingston or Lancaster or Leeds or Leicester or Lichfield or Limerick or Lincoln or Lisburn or Liverpool or London or Manchester or Newcastle or Newport or Newry or Norwich or Nottingham or Oxford or Perth or Peterborough or Plymouth or Portsmouth or Preston or Ripon or St Albans or St Asaph or St David's or Salford or Salisbury or Sheffield or Southampton or Stirling or Stoke or Sunderland or Swansea or Truro or Wakefield or Waterford or Wells or Westminster or Winchester or Wolverhampton or Worcester or York).ti,ab,in.

Term group	#	Searches
	70	or/65-69
	71	(exp africa/ or exp asia/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp oceania/) not (united kingdom/ or europe/)
	72	70 not 71
UK Cost/resource studies	73	64 and 72
UK cost/resource studies published in the last 10 years	74	limit 73 to yr="2008 - Current"
Exclusion criteria	75	Exp Animals/ not exp humans/
	76	(comment or letter or editorial or case reports or clinical trial, phase I).pt.
	77	(case stud$ or case report$).ti.
	78	or/75-77
Total	79	33 or 74
	80	8 and 79
	81	80 not 78

B3. In CS appendices G Table 1 page 190, please explain the reasons for applying a start date of 2008 to the economic review.

A publication date of 2008 onwards was applied only to the UK (or Ireland) cost/resource use results (line 74, **Error! Reference source not found.**). The reason that cost and resource use studies specifically were limited to the past 10 years is to ensure that the most recent data, that are most representative of current

clinical practice were captured. The economic evaluations and health-state utilities streams were not date limited in the search strategy.

Review of existing economic analyses

B4. In CS appendices G Table 1, please clarify why non-UK studies have been excluded from the search strategy?

The UK (and Ireland) search filter (lines 65–72) was applied to the "cost/resource use studies" only (line 73), to ensure only UK (or Ireland)-specific costs were included, as per the NICE reference case and perspective of the economic analysis. No limits were applied to the searches of utility studies or economic evaluations. It should be noted here that while the UK (and Ireland) filter was not applied to the economic evaluations terms, a manual limit was applied to economic evaluations during the screening process to ensure that multinational economic evaluations including the UK (or Ireland) were captured.

B5. Priority question: In CS section B.3.1 page 126, please clarify why only studies which included first-line pembrolizumab plus carboplatin and paclitaxel were included in the review of existing economic studies? Were other previous models identified from the searches used to inform decisions about model structure and/or parameter values (e.g. utilities and health state costs)?

Only economic evaluations that included first-line pembrolizumab plus carboplatin and paclitaxel and took a UK (or Ireland) perspective were eligible for inclusion in the review of economic evaluations, to confirm whether any previous economic evaluations that aligned with the NICE final scope had already been published.

Any studies identified in the utility and HCRU searches which included CE models were used to inform the relevant utility and HCRU parts of the CE model included in this CS but the structure was not. However MSD note that the vast majority of oncology CE models in the advanced lung cancer setting are similar in structure to the model submitted.

Health-related quality of life

B6. Priority question: In CS section B.2.6.6, section B.3.4.2 and the Clinical Study Report (CSR), the clinical review and the CSR only report results from EQ-5D Visual Analogue Scale (VAS) (although the CSR also refers to the EQ-5D-3L questionnaire but does not appear to report results). Page 73 of the CS states that "the EQ-5D VAS PRO, which was used to characterise the utility values included in the cost-effectiveness model." However, page 154 of the CS states "UK preference-based scores were used for all patients analysed from the KEYNOTE-407 clinical trial." Please clarify whether preference-based HRQoL data were collected using the EQ-5D-3L questionnaire and whether these are used in the model.

Model inputs for utility values are based on EQ-5D-3L utility data collected from patients enrolled in the KN407 trial. EQ-5D questionnaire response data were converted to population-based utility values using the UK published algorithm.

B7. Priority question: In CS section B.3.4 page 150, the company's base case model uses utilities based on the patients' time-to-death. However;

(a) HRQoL assessments were conducted during the progression-free phase with a final visit at 30-days after discontinuation (from the CSR). Please clarify the number of patients with EQ-5D-3L assessments before progression and after disease progression at each assessment visit. Please also provide mean EQ-5D-3L utility and confidence intervals for these.

EQ-5D Health Utility Scores (Progression-Free status by IRC Assessment) at Week 3 - UK Algorithm
(Full Analysis Set Population)

	Pembro Combo (N=229)					Control (N=239)					Pooled (N=468)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
On Treatment	[redacted]														
Off Treatment	[redacted]														
Progressive	[redacted]														

n† = Number of patients with non-missing EQ-5D score
m‡ = Number of records with non-missing EQ-5D score
EQ-5D score during baseline is not included
Database cutoff date: 03APR2018

EQ-5D Health Utility Scores (Progression-Free status by IRC Assessment) at Week 6 - UK Algorithm
(Full Analysis Set Population)

	Pembro Combo (N=226)					Control (N=207)					Pooled (N=433)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
On Treatment	[redacted]														
Off Treatment	[redacted]														
Progressive	[redacted]														

n† = Number of patients with non-missing EQ-5D score
m‡ = Number of records with non-missing EQ-5D score
EQ-5D score during baseline is not included
Database cutoff date: 03APR2018

EQ-5D Health Utility Scores (Progression-Free status by IRC Assessment) at Week 9 - UK Algorithm
(Full Analysis Set Population)

	Pembro Combo (N=189)					Control (N=198)					Pooled (N=387)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
On Treatment	[redacted]														
Off Treatment	[redacted]														
Progressive	[redacted]														

n† = Number of patients with non-missing EQ-5D score
m‡ = Number of records with non-missing EQ-5D score
EQ-5D score during baseline is not included
Database cutoff date: 03APR2018

EQ-5D Health Utility Scores (Progression-Free status by IRC Assessment) at Week 12 - UK Algorithm
(Full Analysis Set Population)

	Pembro Combo (N=187)					Control (N=170)					Pooled (N=357)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
On Treatment	[redacted]														
Off Treatment	[redacted]														
Progressive	[redacted]														

n† = Number of patients with non-missing EQ-5D score
m‡ = Number of records with non-missing EQ-5D score
EQ-5D score during baseline is not included
Database cutoff date: 03APR2018

EQ-5D Health Utility Scores (Progression-Free status by IRC Assessment) at Week 15 - UK Algorithm
(Full Analysis Set Population)

	Pembro Combo (N=186)					Control (N=158)					Pooled (N=344)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
On Treatment	[redacted]														
Off Treatment	[redacted]														
Progressive	[redacted]														

n† = Number of patients with non-missing EQ-5D score
m‡ = Number of records with non-missing EQ-5D score
EQ-5D score during baseline is not included
Database cutoff date: 03APR2018

EQ-5D Health Utility Scores (Progression-Free status by IRC Assessment) at Week 18 - UK Algorithm
(Full Analysis Set Population)

	Pembro Combo (N=178)					Control (N=152)					Pooled (N=330)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
On Treatment	[redacted]														
Off Treatment	[redacted]														
Progressive	[redacted]														

n† = Number of patients with non-missing EQ-5D score
m‡ = Number of records with non-missing EQ-5D score
EQ-5D score during baseline is not included
Database cutoff date: 03APR2018

EQ-5D Health Utility Scores (Progression-Free status by IRC Assessment) at Week 27 - UK Algorithm
(Full Analysis Set Population)

	Pembro Combo (N=129)					Control (N=86)					Pooled (N=215)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
On Treatment	[redacted]														
Off Treatment	[redacted]														
Progressive	[redacted]														

n† = Number of patients with non-missing EQ-5D score
m‡ = Number of records with non-missing EQ-5D score
EQ-5D score during baseline is not included
Database cutoff date: 03APR2018

EQ-5D Health Utility Scores (Progression-Free status by IRC Assessment) at Week 36 - UK Algorithm
(Full Analysis Set Population)

	Pembro Combo (N=70)					Control (N=39)					Pooled (N=109)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
On Treatment	[redacted]														
Off Treatment	[redacted]														
Progressive	[redacted]														

n† = Number of patients with non-missing EQ-5D score
m‡ = Number of records with non-missing EQ-5D score
EQ-5D score during baseline is not included
Database cutoff date: 03APR2018

EQ-5D Health Utility Scores (Progression-Free status by IRC Assessment) at Week 45 - UK Algorithm
(Full Analysis Set Population)

	Pembro Combo (N=40)					Control (N=21)					Pooled (N=61)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Progression-free	[redacted]														
On Treatment	[redacted]														
Off Treatment	[redacted]														
Progressive	[redacted]														

n† = Number of patients with non-missing EQ-5D score
m‡ = Number of records with non-missing EQ-5D score
EQ-5D score during baseline is not included
Database cutoff date: 03APR2018

(b) Please summarise all estimates of pre-progression and post-progression utility values from the studies identified as part of your HRQoL review.

The results of the three studies identified that reported pre-progression and post-progression utility values are summarised in the Table below. Full details of these three studies are provided in the Table following this.

Summary of pre-progression and post-progression utility values identified in the health state utility study review

Source (study/ publication, publication year)	**Pre-progression utility values**	**Post-progression utility values**
Chouaid et al. 2013 [5]	Mean (SD) [95% CI] EQ-5D utility scores for patients on first-line treatment: • Progression free (n=115): 0.71 (0.24) [0.67, 0.76]	Mean (SD) [95% CI] EQ-5D utility scores for patients on first-line treatment: • Progressive disease (n=26): 0.67 (0.20) [0.59, 0.75]
Khan et al. 2015 [6]	Mean (SE) EQ-5D utility scores of NSCLC patients receiving treatment with: • Erlotinib (n=334): 0.6482 (0.009) • Placebo (n=313): 0.6438 (0.011) Mean (SE) EQ-5D utility scores of the sub-population of NSCLC patients that developed a rash during their first treatment cycle: • Erlotinib (n=334): 0.6407 (0.017) • Placebo (n=313): 0.6193 (0.015)	Mean (SE) EQ-5D utility scores of NSCLC patients receiving treatment with: • Erlotinib (n=334): 0.5517 (0.016) • Placebo (n=313): 0.5760 (0.014) Mean (SE) EQ-5D utility scores of the sub-population of NSCLC patients that developed a rash during their first treatment cycle: • Erlotinib (n=334): 0.5548 (0.0255) • Placebo (n=313): 0.5756 (0.020)
NICE HTA (TA500) [7]	Least squares mean (95% CI) EQ-5D utility score for progression-free patients following treatment with: • Ceritinib: 0.81 (NR)	NR

Summary of EQ-5D utility studies for patients in first-line treatment included in the economic systematic literature review (taken from Table 13 appendix G in the CS)

Source (study/ publication, publication year)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
Chouaid et al. 2013 [5]	Adult patients previously diagnosed with advanced (stage IIIB/IV) NSCLC and had received two cycles of their current pharmacotherapy (equivalent to six to eight weeks ± three days of therapy). Patients were enrolled in the patient survey between April 2010 and August 2011 by their treating physician (n=263): • Mean (SD) age: 64.7 (10.1) years • 61.2% of patients were male	International: Australia, Belgium, Canada, France, Italy, Turkey, The Netherlands, Sweden, and the UK.	319 patients were enrolled in the study. 263 patients met the inclusion criteria and completed the EQ-5D. 145/263 (55.1%) patients were receiving first-line treatment.	Utility value estimates of patients with advanced NSCLC who were either progression-free or had progressive disease. Utility values associated with adverse events were not reported.	Patients completed the questionnaires at the study site and the physician or study nurse completed a questionnaire with information on the patient's past and current treatment and response to the actual treatment line. The UK-specific value set was used to convert the EQ-5D health state descriptions to the EQ-5D index score.	**Mean (SD) [95% CI] EQ-5D utility scores for patients on first-line treatment:** • **Progression free (n=115):** 0.71 (0.24) [0.67, 0.76] • **Progressive disease (n=26):** 0.67 (0.20) [0.59, 0.75] Note that utilities were also presented for second and third line treatments as well as BSC but only first line treatment scores were eligible here.	**Consistency with NICE reference case:** EQ-5D health state descriptions were elicited directly from patients, and were valued using the UK value set, reflecting the preferences of the UK general population. **Relevance to the decision problem:** Utility value estimates for patients with advanced NSCLC on their first line of active treatment. However, as the treatment

<table>
<tr><th>Source (study/ publication, publication year)</th><th>Description of population and recruitment method</th><th>Country</th><th>Sample size and response rate</th><th>Health states and adverse events</th><th>Methods of elicitation & valuation</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation</th></tr>
<tr><td></td><td>• 55.1% of patients were on first-line treatment</td><td></td><td></td><td></td><td></td><td></td><td>received was unclear the values may be less relevant to the current cost-effectiveness evaluation.</td></tr>
<tr><td>Khan et al. 2015 [6]</td><td>Patients were part of the double-blind, placebo-controlled, phase III RCT TOPICAL trial that evaluated the efficacy of erlotinib in chemotherapy-naïve patients with stage IIIb–IV NSCLC. Erlotinib or placebo was given in addition to best supportive care.

Patients were enrolled between 2005 and 2009.</td><td>UK</td><td>Total patients randomised: 670

334/350 of patients randomised to the erlotinib treatment arm received treatment and were included in the analysis.

313/320 of patients randomised to the placebo arm were included in the analysis.</td><td>Utility value estimates of patients with advanced NSCLC treated with erlotinib or placebo before and after disease progression.

Utility value estimates of patients with advanced NSCLC treated with erlotinib or placebo that developed a rash during their first treatment cycle.</td><td>EQ-5D-3L responses were collected from patients at baseline and every month in the first year and 6 monthly thereafter until disease progression or death.

Responses were captured on paper case report forms during clinical assessment.

The UK-specific value</td><td>Mean (SE) EQ-5D utility scores of NSCLC patients pre- and post-disease progression:
<table><tr><th></th><th>Erlotinib (n=334)</th><th>Placebo (n=313)</th></tr><tr><td>Pre-progression</td><td>0.6482 (0.009)</td><td>0.6438 (0.011)</td></tr><tr><td>Post-progression</td><td>0.5517 (0.016)</td><td>0.5760 (0.014)</td></tr></table>Mean (SE) EQ-5D utility scores of the sub-population of NSCLC patients that developed a rash during their first treatment cycle:</td><td>Consistency with NICE reference case: EQ-5D health state descriptions were elicited directly from patients, and were valued using the UK value set, reflecting the preferences of the UK general population.

Relevance to the decision problem: Utilities are presented for NSCLC patients pre- and post-</td></tr>
</table>

<table>
<tr><th>Source (study/ publication, publication year)</th><th>Description of population and recruitment method</th><th>Country</th><th>Sample size and response rate</th><th>Health states and adverse events</th><th>Methods of elicitation & valuation</th><th>Utility values and uncertainty around values</th><th>Appropriateness of study for cost-effectiveness evaluation</th></tr>
<tr>
<td></td>
<td>Baseline characteristics for patients in the erlotinib treatment arm (n=350):
Median (range) age: 77 (45–91) years
135 (39%) of patients were female
Baseline characteristics for patients in the placebo arm (n=320):
Median (range) age: 78 (51–91)
126 (39%) of patients were female</td>
<td></td>
<td>The objective of the study was to assess the cost-effectiveness of erlotinib compared with placebo in combination with best supportive care across the overall study population as well as for a predefined subgroup of patients that developed a rash during treatment.

178/334 patients that received erlotinib developed a rash in their</td>
<td></td>
<td>set was used to convert the EQ-5D health state descriptions to the EQ-5D index score.</td>
<td><table><tr><th></th><th>Erlotinib (n=178)</th><th>Placebo (n=278)</th></tr><tr><td>Pre-progression</td><td>0.6407 (0.017)</td><td>0.6193 (0.015)</td></tr><tr><td>Post-progression</td><td>0.5548 (0.0255)</td><td>0.5756 (0.020)</td></tr></table>The differences between the EQ-5D index scores of patients in the erlotinib and placebo arms at pre- and post-progression were not significant for both the overall study population and subgroup of patients that developed a rash.</td>
<td>progression after receiving best supportive care plus placebo, which may be relevant for the current cost-effectiveness evaluation.</td>
</tr>
</table>

Source (study/ publication, publication year)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
			first treatment cycle. 278/313 of patients that received placebo developed a rash in their first treatment cycle. Approximately 98% of EQ-5D forms were completed at baseline.				
NICE HTA (TA500) [7]	Patients were part of the ASCEND-4 a phase III, open-label, randomised controlled trial comparing ceritinib to platinum-based chemotherapy	International: 134 sites in 28 countries: Australia, New Zealand, Austria, Brazil, China, Colombia, Denmark,	≥80% patients completed the questionnaires at most time points. 180 patients in the ceritinib treatment arm completed the EQ-5D	Utility value estimates of patients with advanced NSCLC following treatment with: • Ceritinib • Chemotherapy Utility value estimates of	Patients completed the EQ-5D by self-report. The UK-specific value set was used to convert the EQ-5D health	**Least squares mean (95% CI) EQ-5D utility score:** • **Ceritinib:** 0.8132 (0.78408, 0.84231) • **Chemotherapy:** 0.7708 (0.73905, 0.80264) • **Progression free (stable disease or objective response) receiving ceritinib treatment:** 0.81 (NR)	**Consistency with NICE reference case:** EQ-5D health state descriptions were elicited directly from patients, and were valued using the UK value set,

Source (study/ publication, publication year)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	(cisplatin or carboplatin plus pemetrexed, followed by pemetrexed maintenance therapy) in treatment-naïve, adult patients with non-squamous, stage IIIB or stage IV ALK-positive NSCLC patients. Ceritinib group (n=189): • Median (range) age: 55 (22–81) years • 54% of patients were female Chemotherapy group (n=187): • Median (range) age:	France, Germany, Greece, India, Ireland, Italy, Japan, South Korea, Lebanon, Mexico, Netherlands, Norway, Portugal, Russia, Singapore, Spain, Sweden, Taiwan, Thailand, Turkey, and the UK.	questionnaire during treatment. 159 patients in the chemotherapy treatment arm completed the EQ-5D questionnaire.	progression-free patients with advanced NSCLC following treatment with certinib. Utility values associated with adverse events were not reported.	state descriptions to the EQ-5D index score.		reflecting the preferences of the UK general population. **Relevance to the decision problem:** Utility values for advanced NSCLC receiving first-line ceritinib or chemotherapy are presented, which may be less relevant to the current cost-effectiveness evaluation.

Source (study/ publication, publication year)	Description of population and recruitment method	Country	Sample size and response rate	Health states and adverse events	Methods of elicitation & valuation	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	54 (22–80) years • 61% of patients were female						

(b) Within the CS, the rationale for adopting the time-to-death utility approach is justified as it "offers a better HRQoL data fit." However, the CS also highlights that within the KEYNOTE-407 trial, utility data were collected only until drug discontinuation or the 30-day post-study safety follow-up visit. Please comment on how this method addresses potential issues relating to informative censoring.

While we do not have data from beyond the time points where the EQ-5D was administered in the trial, given that there was no statistically significant difference in utilities by treatment arm for each time-to-death health state within the trial, one would not a priori expect to find a difference in utilities for these states between patients pre- and post-discontinuation. It is difficult to know whether utilities collected with a longer time horizon would produce different values. One might not expect this for patients <365 days from death, but utilities might be higher for patients >365 days from death in the long term, if surviving patients are completely cured of their lung cancer/ in full remission and off treatment. Thus, it is possible that the cost-effectiveness of extending survival could be conservatively estimated in the model if utilities are under-estimated for this health state.

B8. In the submitted model, on worksheet "Utility Inputs", cells C122:G130 values appear to be from Kind et al (https://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf), rather than from Ara and Brazier (Value in Health, 2010, as reported in the CS). However, the values do not match age and sex-specific values reported in Table A in Kind et al. Please clarify. Please also clarify what the values in cells D33:D208 represent, their source and how they are used in the model.

The submitted model was using general population utilities adjusted by age only rather than age and gender. In the updated model, the coefficients reported in Ara and Brazier, published in the referenced paper are reported and the calculations to estimate the utility values by age and gender shown. Cells C122:G130 reported estimated utilities for the general population by treatment group, only the utility for age 75+ from this table (Cell G130) is used in the model to estimate the annual utility decrement for age 75+ vs. baseline age. Cells D33:F208 show the estimated utilities

by age using the coefficients reported in the Ara and Brazier, 2010 publication. These are used the estimate the annual utility decrement.

B9. Priority question: In the submitted model, on worksheets "NMA-ITC PFS (conHR)" and "NMA-ITC OS (conHR)", with respect to the NMAs used in the model;

(a) Please clarify which NMA has been used to inform the model (this appears to be the squamous PD-L1 unselected group but is not clear).

Yes, the squamous PD-L1 unselected NMA is used in the model.

Please clarify why the hazard ratios reported in CS Tables 33 and 34 do not match the point estimates used in the model NMA worksheets.

Apologies for the confusion, the values in the model differ from tables 33 and 34 and are available in the reference submitted with the clarification letter response – a separate NMA report combining the platinum regimens when paired with a common treatment which is how they were inputted into the CE model (e.g., platinum + gemcitabine rather than cisplatin plus gemcitabine and carboplatin plus gemcitabine separately).

(b) Please provide Convergence Diagnostic and Output Analysis (CODA) samples from the NMA for 1,000 iterations in order to account for correlations between treatment effects.

Please refer to excel documents uploaded with this response.

B10. In CS section B.3.2.3 page 136, it states "In addition, there is evidence to suggest that paclitaxel and nab-paclitaxel are not significantly different in terms of OS[39]." The cited study does not appear to mention nab-paclitaxel – please clarify whether the study does include nab-paclitaxel. In addition, please comment on whether there is evidence to suggest the same is true for PFS.

Apologies, the reference should have been: *Socinski MA, Bondarenko I, Karaseva NA, Makhson AM, Vynnychenko I, Okamoto I, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: Final results of a phase III trial. Journal of Clinical Oncology. 2012;30(17):2055-62* [8] which states there

was a 1-month increase in OS in the nab-paclitaxel arm versus the paclitaxel arm (HR, 0.922;95%CI, 0.797 to 1.066; *P*_.271; Fig 2B). Median OS was 12.1 months (95% CI, 10.8 to 12.9 months) in the nab-paclitaxel arm compared with 11.2 months (95% CI, 10.3 to 12.6 months) in the paclitaxel arm. The OS in the nab-paclitaxel arm was noninferior to the OS in the paclitaxel arm (HRnab-Pac/Pac 95% CI upper bound, 1.066).

B11. In CS section B.3.2.3 page 136, it states "In line with the comparator assessed in KEYNOTE-407, Standard of Care (SoC) (based on the trial chemotherapy arm) was considered as the comparator of relevance in the cost-effectiveness model. It is noted that the comparator arm in KEYNOTE-407 has only a small market share in UK clinical practice (2%). Since there is a lack of published data in this patient population, and based on evidence detailed in section B.2.8 it was assumed that the comparator arm in KEYNOTE-407 is equivalent to other platinum chemotherapy options available in the UK with which clinical experts have agreed."

(a) Please comment on whether you believe that there is a difference between the regimens or that all regimens have the same efficacy?

As mentioned in the CS, based on published literature [9] and feedback from UK clinical oncologists, it has been assumed that all SoC regimens have the same efficacy in the patient population being assessed in this TA.

(b) Please clarify why all of the options included in the NMA have not been included in the model (e.g. why are vinorelbine containing regimens excluded?)

As can be seen in the network diagram in Figure 21 of the CS, in the squamous PD-L1 unselected network, no relevant trial data for vinorelbine plus cisplatin or carboplatin was identified.

(c) Please clarify where the 2% value included in the quote came from. The IPSOS data provided as part of the submission appears to suggest that carboplatin/paclitaxel has a market share of 7%.

The 2% value is a typo from a previous market share time cut. The most recent and utilised value is 7%.

(d) Please provide further detail regarding the clinical judgements supporting this view.

As detailed in the CS, during the appraisal of TA411, the committee agreed with clinical experts in that platinum-based regimens (gemcitabine, vinorelbine, docetaxel or paclitaxel) were all very similar in efficacy in previously treated advanced squamous NSCLC. A paper by Schiller et al [9] describes a comparison of four platinum based chemotherapy options for advanced NSCLC which concludes that "none of the four chemotherapy regimens offered a significant improvement over the others". Furthermore, discussions with 2 clinical experts during this appraisal has also concluded that the comparator arm in KEYNOTE-407 can be considered equivalent to other available platinum based chemotherapy options. The clinical experts also referred to the aforementioned Schiller paper.

Model assumptions

B12. Priority question: In CS section 3.2.3 Table 56 page 134, the model applies a constant treatment effect for pembrolizumab indefinitely. Please provide evidence that discontinuing pembrolizumab at 2 years does not lead to a loss of treatment effect.

There is no evidence to suggest that discontinuing pembrolizumab at 2 years does lead to a loss of treatment effect. MSD have previously provided scenarios in which treatment waning is investigated from year 5 (scenario 9 of the CS). Data from a publication from Herbst et al [10] investigating long-term survival of patients with advanced NSCLC in KEYNOTE-010 who completed 2 years of treatment with pembrolizumab. It concluded that most patients who completed 35 cycles or 2 years of pembrolizumab therapy had durable response, with ongoing response in 64% of patients at median follow-up of 43.4 months.

B13. Priority question: In CS section B.2.6.2 Figure 4 page 52, the figure indicates that the OS curves for pembrolizumab plus chemotherapy versus chemotherapy alone nearly intersect at around 17 months. However, the model suggests that

differences observed at earlier time points in KEYNOTE-407 are maintained indefinitely due to the use of a constant HR. Please justify this assumption.

The data at tail of the KM curve reflect very sparse observations, which from a modeling perspective should be permitted to have little or no impact on the extrapolation regardless of the method used, and this is true of both the parametric and base case population-based (SEER) approaches used. Thus, in the instance of the population-based extrapolation method, there is simply insufficient data to conclude a further trend in OS beyond the period of the KM data modeled.

B14. Priority question: In CS section 3.2.2 page 133, it states that "In addition, cross over from the SoC arm to pembrolizumab was allowed during the trial but since 2L IO therapy is standard of care in the UK for patients with squamous NSCLC 94 27 107, cross over adjustment has not been implemented in the Intention To Treat (ITT) base case analysis." Please clarify the proportion of patients randomised to standard care who went on to have second-line immunotherapy who were PD-L1 <1%, 1-49% and ≥50%.

While a total of 75/281(26.7%) patients switched over to pembrolizumab monotherapy within the by-protocol allowed switching-over scenario, another 14 switchover events occurred indirectly – to another PD-L1 treatment.

In subjects with PD-L1 TPS >= 50%, 73 patients were randomized to the control arm and 23 patients out of these (31.5%) switched over to pembrolizumab monotherapy and 6 indirect. In subjects with PD-L1 TPS 1% - 49%, 104 patients were randomized to the control arm and 28 (26.9%) of these patients switched over to pembrolizumab monotherapy and 5 indirect. In subjects with PD-L1 TPS <1%, 99 patients were randomized to the control arm and 23 (23.2%) out of these patients switched over to pembrolizumab monotherapy and 3 indirect.

Extrapolation

B15. In CS appendices L page 294, it states "As also discussed in Document B, standard parametric curves were initially fitted to the Kaplan-Meier (KM) OS data and subsequently deemed clinically implausible." Please clarify whether the fitting of the

parametric curves refers to the use of a piecewise approach with a changing point. Please elaborate on why these curves were deemed clinically implausible.

The fitting of parametric curves does refer to the use of a piecewise approach with a cut point of week 19 for OS. As per the CS, it was found that standard statistical-based fitting utilising data from within the period of the trial provides potentially clinically implausible OS results for the SoC arm of 1-2% at 5 years. It is thought that this is unrealistic given the advances in care in this patient population and the introduction of 2L IO therapy. In a recent NICE TA in this patient population in second line [11], the committee agreed that the OS for 2L patients who would receive the assessed treatment would be 16.06 months. It can be assumed then that in addition to 4 cycles of 1L platinum chemotherapy available as the 1L SoC for these patients would bring this to around 19 months. Although, equivalence between the KEYNOTE-407 and clinical trial utilised in the aforementioned TA (Checkmate-017) cannot be inferred, the patient characteristics and potential outcomes can be considered broadly similar for at least the 52% of the KEYNOTE-407 population who go on to receive a 2L therapy following SoC in the economic model.

Although not in the same patient population, but with inclusion of squamous histology patients in the clinical trial, during TA447 and its review (TA531) [12], the ERG preferred a time cut which produced an estimate of 9.6% survival at 5 years and 1.5% at 10 years due to the availability of IO drugs in 2L SoC for the PD-L1 positive patients even suggesting 5 year estimates could be as high as around 17%. The ERG also mentioned the CRUK data of 10% alive at 5 years and 5% at 10 years. However OS at stage 4 is not available as there are such a small number of people surviving more than 2 years [13].

B16. Priority question: Please provide the empirical hazard plot for each arm for the following trials (first mentioned – section B.1.1 table 1 page 15 and section B.2.2 page 29):

- KEYNOTE-407 (ITT and PD-L1 <1%, 1-49% and ≥50% subgroups, including before and after weighting for the ≥50% subgroup),
- KEYNOTE-042 squamous and PD-L1 strong expression (TPS ≥50%) patients (both before and after weighting),

- KEYNOTE-024 squamous and PD-L1 strong expression (TPS ≥50%) patients (both before and after weighting).

The following plots for hazard functions over time are descriptive. The limited robustness of such estimates suggests a special caution in the interpretion of these results. Usual hazard ratios should be considered for any assessment of the treatment effects.

The hazard functions are displayed in the following figures:

- Overall survival of the study KN407: The estimated instantaneous risks over time of death were generally smaller among patients in Pembrolizumab + Chemotherapy arm compared to the same risks among patients in the Chemotherapy arm. This finding was consistent across the three PD-L1 expression defined populations (TPS <1%, TPS 1-49% and TPS ≥50%). The exception was for patients with TPS ≥50% after weighting, where the risk for patients in Control arm fell below the risk for patients in Pembrolizumab + Chemotherapy arm after month 11. However the estimates are less robust over time as the number of patients at risk are smaller.
- Progression-free survival of the study KN407: The findings for PFS are like OS. The exception was for patients with TPS 1-49% where the risks for patients in Pembrolizumab + Chemotherapy and Control arms were similar at the last event time point.
- For study KN042 patients with TPS ≥50% overall survival and progression-free survival. Overall, smaller risks were observed in patients Pembrolizumab Monotherapy arm versus patients in Chemotherapy arm. Furthermore, a linear decrease over time of the risk of event was observed for patients in the Pembrolizumab Monotherapy arm, consistently both for OS and PFS, before and after weighting. Such a clear pattern was not identified for Chemotherapy arm.
- For KN024, there were only 10 subjects, therefore no robust estimates for hazard functions could be obtained.

KEYNOTE-407

Overall Survival

Hazard functions
Overall Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
ITT Population
TPS <1%
(Study 407)

Hazard functions
Overall Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
ITT Population
TPS 1-49%
(Study 407)

Hazard functions
Overall Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
Before Weighting
ITT Population
TPS ≥ 50%
(Study 407)

Hazard functions
Overall Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
After Weighting
ITT Population
TPS ≥ 50%
(Study 407)

Progression Free Survival based on IRC assessment per RECIST 1.1

Hazard functions
Progression-Free Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
ITT Population
TPS <1%
(Study 407)

Hazard functions
Progression-Free Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
ITT Population
TPS 1-49%
(Study 407)

Hazard functions
Progression-Free Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
Before Weighting
ITT Population
TPS ≥ 50%
(Study 407)

Hazard functions
Progression-Free Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
After Weighting
ITT Population
TPS ≥ 50%
(Study 407)

KEYNOTE-042

Overall Survival

Hazard functions
Overall Survival
Comparison of Pembrolizumab vs. Chemotherapy
Before Weighting
ITT Population
TPS ≥ 50%
(Study 042)

Hazard functions
Overall Survival
Comparison of Pembrolizumab vs. Chemotherapy
After Weighting
ITT Population
TPS ≥ 50%
(Study 042)

Progression Free Survival based on IRC assessment per RECIST 1.1

Hazard functions
Progression-Free Survival
Comparison of Pembrolizumab vs. Chemotherapy
Before Weighting
ITT Population
TPS ≥ 50%
(Study 042)

Hazard functions
Progression-Free Survival
Comparison of Pembrolizumab vs. Chemotherapy
After Weighting
ITT Population
TPS ≥ 50%
(Study 042)

B17. Priority question: Please provide the log cumulative versus log time plot to assess the proportional hazards assumption for OS and PFS for the following trials (first mentioned – section B.1.1 table 1 page 15 and section B.2.2 page 29):

- KEYNOTE-407 (ITT and PD-L1 <1%, 1-49% and ≥50% subgroups, including before and after weighting for the ≥50% subgroup),
- KEYNOTE-042 squamous and PD-L1 strong expression (TPS ≥50%) patients (both before and after weighting),
- KEYNOTE-024 squamous and PD-L1 strong expression (TPS ≥50%) patients.

The proportional hazards assumption for OS and PFS before and after weighting was assessed using the Grambsch and Therneau approach, 1994. Both a graphical inspection and test statistic were provided for KEYNOTE 407 and KEYNOTE 042. Data from KEYNOTE 024 were not included in the indirect comparison as only 10 patients qualified the criteria of squamous and pre-assigned to platinum+paclitaxel (see also A22). Hence the proportional hazards assumption was not assessed for this subset of KEYNOTE 024.

KEYNOTE-407

Overall Survival

Test of Proportional Hazard assumption based on Grambsch and Therneau
Overall Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
ITT Population
TPS <1%
(Study 407)

	rho	chisq	p-value
Overall Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 03APR2018			

[redacted]

Test of Proportional Hazard assumption based on Grambsch and Therneau
Overall Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
ITT Population
TPS 1-49%
(Study 407)

	rho	chisq	p-value
Overall Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 03APR2018			

[redacted]

Test of Proportional Hazard assumption based on Grambsch and Therneau
Overall Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
Before Weighting
ITT Population
TPS ≥ 50%
(Study 407)

	rho	chisq	p-value
Overall Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 03APR2018			

Test of Proportional Hazard assumption based on Grambsch and Therneau
Overall Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
After Weighting
ITT Population
TPS ≥ 50%
(Study 407)

	rho	chisq	p-value
Overall Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 03APR2018			

Progression Free Survival based on IRC assessment per RECIST 1.1

Test of Proportional Hazard assumption based on Grambsch and Therneau
Progression-Free Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
ITT Population
TPS <1%
(Study 407)

	rho	chisq	p-value
Progression Free Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 03APR2018			

[redacted]

Test of Proportional Hazard assumption based on Grambsch and Therneau
Progression-Free Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
ITT Population
TPS 1-49%
(Study 407)

	rho	chisq	p-value
Progression Free Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 03APR2018			

Test of Proportional Hazard assumption based on Grambsch and Therneau
Progression-Free Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
Before Weighting
ITT Population
TPS ≥ 50%
(Study 407)

	rho	chisq	p-value
Progression Free Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 03APR2018			

Test of Proportional Hazard assumption based on Grambsch and Therneau
Progression-Free Survival
Comparison of Pembrolizumab + Chemotherapy vs. Chemotherapy
After Weighting
ITT Population
TPS ≥ 50%
(Study 407)

	rho	chisq	p-value
Progression Free Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 03APR2018			

KEYNOTE-042

Overall Survival

Test of Proportional Hazard assumption based on Grambsch and Therneau
Overall Survival
Comparison of Pembrolizumab vs. Chemotherapy
Before Weighting
ITT Population
TPS ≥ 50%
(Study 042)

	rho	chisq	p-value
Overall Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 26FEB2018			

Test of Proportional Hazard assumption based on Grambsch and Therneau
Overall Survival
Comparison of Pembrolizumab vs. Chemotherapy
After Weighting
ITT Population
TPS ≥ 50%
(Study 042)

	rho	chisq	p-value
Overall Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 26FEB2018			

[redacted]

Progression Free Survival based on IRC assessment per RECIST 1.1

Test of Proportional Hazard assumption based on Grambsch and Therneau
Progression-Free Survival
Comparison of Pembrolizumab vs. Chemotherapy
Before Weighting
ITT Population
TPS ≥ 50%
(Study 042)

	rho	chisq	p-value
Progression Free Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 26FEB2018			

Test of Proportional Hazard assumption based on Grambsch and Therneau
Progression-Free Survival
Comparison of Pembrolizumab vs. Chemotherapy
After Weighting
ITT Population
TPS ≥ 50%
(Study 042)

	rho	chisq	p-value
Progression Free Survival	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 26FEB2018			

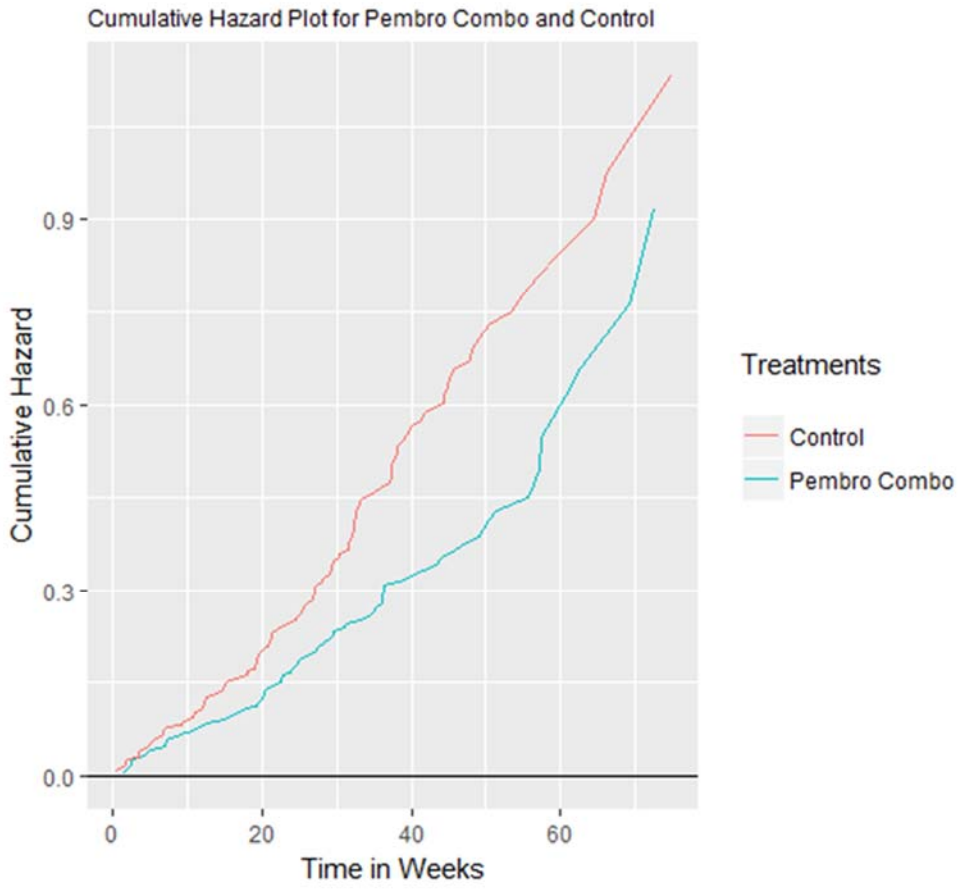
[redacted]

KEYNOTE-024

Only 10 subjects, therefore no robust estimates for PH assumption assessment.

B18. In CS appendices L page 300, it states "Given that the changes in slope, as part of the cumulative hazard plot, were more pronounced in the SoC arm." The log-log plot appears to suggest a broadly constant rate. Please clarify where this change in slope occurs.

As per appendices L, the cumulative hazard plot is shown below. It is true that there is a broadly constant rate however statistical testing and the Schoenfeld plot (available in appendix L also) shows that the proportional hazards assumption does not hold and so then investigating the plot, a change in the slope can be seen in the control arm around week 25-30 although marginal. This cut point also provided a good level of trial data after the cut point. Scenario analysis are also available in the model +/- 10 weeks.



B19. Please provide clinical rationale for the change of hazard at week 19 for overall survival and the change of hazard at week 26 for progression-free survival in both SoC arm and pembrolizumab combined arm in KEYNOTE-407 (first mentioned – section B.1.1 table 1 page 15).

MSD cannot offer any further clinical rationale for why the hazard changes at week 19 and 26 for OS and PFS respectively. The reasons for the choice of these cut points are discussed here. As discussed in appendices L, an examination of Chow test plots for OS reveal a very late time point (week 57) for the most notable change in the hazard for the pembrolizumab combination arm and a peak plot value at week 19 for the SoC arm. As there are only 7 death events in the pembrolizumab combination arm following week 57, and only 1 or 2 events within several PD-L1 sub-groups, the week 57 cut-point was deemed to be too late to provide for valid extrapolations, and a review of the cumulative hazard plot did not identify an earlier cut-point with sufficient subsequent events. This was not an issue for the SoC arm with a week 19 cut-point. A week 19 cut-point was therefore chosen for both trial arms for initially exploring extrapolation of OS with cut points before and after this also investigated (week 9 and 29).

For PFS, evaluation of the data within each trial arm in the overall population via an inspection of output from Chow tests and cumulative hazard functions suggests that there are further substantive changes in the slope in the PFS hazard function beyond week 6 which would have a similar effect. To enable satisfactory curve-fitting, trial KM data are used in the model base case until week 26 (two additional time points at weeks 16 and 36 were also considered in scenario analysis) in both the pembrolizumab combination arm and SoC arms, followed by parametric functions. These cut-points are chosen based on Chow test results, suggesting the most notable changes in the slope of the hazard for each comparator occur near this time point. In recent survival analysis guidance[14] and echoed in recent NICE TAs [12], the Evidence Review Group (ERG) has preferred this approach to fitting a parametric function distribution over an entire model time horizon.

B20. Please provide details on how Chow test (first mentioned –CS section B.3.10.1 page 196) was performed for the time-to-event data, in particular, how the censoring was dealt with

The Chow test is used to identify any potential structural change in the cumulative hazard at any specific time point. The idea behind conducting this test is to identify the time points and perform a two-piece (KM+parametric) fitting. The Chow test is used to test the heterogeneity between two (or more) regressions. The basic underlying distribution assumption is exponential. It is used it as a potential-structural-change detector. Other methods like eyeballing and biological reasoning need to be considered as well to determine final cutoffs.

The platform for chow test is based on obtaining the conditional probability of survival say S(t)=P(T>t|T<=t), which is also the Kaplan-Meier. The dependent variable is -log(S(t)) (cumulative hazard). When obtaining S(t), the censored subjects are looked after. The three regressions that are being tested are 2 unrestricted and 1 restricted as below:

Data; full dataset

Data1; dataset with time points greater than the cut-off point 'c' (c may be 9,15,21,27 etc. in weeks)

Data2; dataset with time points less than or equal than the cut-off point 'c'

r.reg = lm(-log(S(t))~time, data)

ur.reg1 = lm(-log(S(t))~time, data = Data1)

ur.reg2 = lm(-log(S(t))~time, data = Data2)

lm; fits linear model in R with –log(S(t)) as the dependent variable

where S(t) is the conditional probability of survival at any time t. The calculation of S(t) itself incorporates the observed censoring in the trial data.

The test statistic is given by:

Chow= Numerator/Denominator

Where; Numerator= [S1−(S2+S3)]/k and Denominator= [(S2+S3)/(n−2k)]

Where S1 is sum of squares regression for restricted regression, S2 and S3 are the sum of squares of two unrestricted regression respectively.

'k' being the number of parameters estimated, including the intercept and 'n' being number of observations.

The test statistic Chow ~ F(k, n-2k)

B21. In CS appendices L figure L6 page 305, please clarify if this analysis uses a joint model including a treatment-indicating covariate, or whether separate models have been fitted to each trial arm. In addition, the text states "The cut-off time points provide a good balance of KM data to be used directly in the first phase and enough remaining events 79% events still remaining in the SoC arm to be used to fit a curve in the second phase." Please also clarify the number of remaining events in the pembrolizumab arm after the 26-week cut-point.

Separate models were fitted to each trial arm with no treatment indicating covariate. The number of events remaining in the pembrolizumab arm after the week 26 cut point was 142 according to Table L.4 in the CS appendices.

B22. Priority question: In CS section B.3.3.1 page 139, arguments made around using SEER data in favour of data from KEYNOTE-407 to extrapolate outcomes for the comparator group are based on the view that mortality risk does not follow a constant rate. Please clarify:

(a) Why an alternative model fitted to the KEYNOTE data with a non-constant hazard rate was not used instead?

A non-constant HR model would be less ideal as it cannot capture changing trends in mortality originating beyond the trial follow-up period and would be asking a great deal of the limited trial data available to be able to accurately predict this. It would also be unclear how to appropriately fit such a model. The best fitting model based on AIC/BIC with a non-constant hazard could still perform quite poorly relative to population data, clinical plausibility or further trial data to become available. The SEER data utilised is a real world evidence source and hence could be considered

more reliable than a statistical extrapolation based on limited trial follow up and also allows for population generalisability and clinical plausibility.

In addition, a recent study by Vickers et al [15] evaluated survival curve extrapolation techniques using long-term observational cancer data. The results from this study support the direct use of external data to extrapolate survival curves even when the external data may not be an exact match with the RCT data further supporting the use of SEER data to extrapolate outcomes in the CS.

An additional recent study from Bullemont et al[16] investigated how the overall survival extrapolation initial estimates in health technology assessments of cancer immunotherapy by NICE compare with subsequent available trial data. The study concluded that the initial OS extrapolations employed by manufacturers and ERGs generally predicted OS reasonably well when compared to more mature data (when available), though on average they appeared to underestimate OS. This review and validation shows that while the choice of OS extrapolation is uncertain, the methods adopted are generally aligned with later-published follow-up data and appear appropriate for informing HTA decisions. Whilst the OS extrapolation methods employed in the studies included here might have varied from the base case method presented, this does suggest that the long-term OS estimates presented in the CS are likely an underestimate if anything.

(b) Why external data are deemed necessary to inform OS outcomes. Is this because (i) the data from KEYNOTE-407 are too limited due to short follow-up and limited numbers of events, or (ii) KEYNOTE-407 is not generalizable to clinical practice in England?

The data from KEYNOTE-407 are based on limited follow up and numbers of events.

(c) The extent to which the SEER data will reflect outcomes for patients who receive immunotherapies which are available in the first- and second-line settings in the UK.

As described in the CS, in the UK, the National Lung Cancer Audit (NLCA) looks at the care delivered for people diagnosed with lung cancer and mesothelioma in England, Wales and Scotland, and therefore, survival estimates reported in NLCA can be considered representative of UK clinical practice however published estimates are only

available for one year survival in the all histologies NSCLC population [17]. MSD contacted the NLCA in order to obtain further longer term UK data if available and have so far been unable to do so. SEER is a co-ordinated system of population based cancer registries located across the US; data are collected on cancer incidence and survival from 18 geographic areas comprising nearly 30% of the US population, and the population covered by SEER is comparable to the general US population [18].

Given that NLCA data were only available for up to 1 year, SEER registry data were an important source for extrapolation of the long-term survival projections. The comparability of US and UK cancer statistics were assessed by undertaking a comparison of key epidemiological and mortality trends, as reported in the Tables below. The UK NLCA data is reported from time of diagnosis. Within the KEYNOTE-407 mortality risk adjustment using SEER utilised in this economic evaluation, data were taken from SEER post 2 months from diagnosis to be in line with the KEYNOTE-407 trial protocol [19] . In the Table below, SEER data has been adjusted to time from diagnosis to provide a more like for like comparison with the NLCA estimates. This assessment revealed that, in general, epidemiological and survival statistics are consistent across the UK and US for lung cancer. Specifically, for incidence, deaths, mortality, and proportion alive by year, as well as the stage distributions at diagnosis and trends in age at diagnosis are consistent across populations in the UK and the US. Additionally, baseline characteristics of patients registered in the KEYNOTE-407 trial were compared with those of patients in the SEER and NLCA registries, and this comparison is presented in the third table. A limitation in the comparison is the lack of data describing patients by line of therapy, type of therapy and performance status, however, the overall conclusion is that the baseline demographics of UK and US registries are not dissimilar to each other and the trial patients providing further justification for the long-term extrapolations based on these RWD. Discussions with UK clinical oncologists also felt that the use of this data in the absence of UK data should be considered robust.

Comparison of UK and US data for lung cancer

	UK	US
Incidence	71.2 per 100,000 (2015) [20]	54.6 per 100,000 (2015) [21]
Estimated new cases	13% of all cancers [20]	13.5% of all cancers[21, 22]
Estimated Deaths	19,314 (2016) – 21% of all cancer deaths[23]	154,050 (2018) – 25% of all cancer deaths
Mortality	54.3 per 100,000	43.4 per 100,000

Proportion alive 1 year (stage IV)	15.5%[17]	23.8%
Proportion alive 5 years (stage IV)	Not available	3.0% [21]

Comparison of stage distribution for lung cancer across the UK and US

Stage %	I	II	III	IV	Unknown
UK[20]	15%	7%	19%	48%	10%
US[21]	16%		22%	57%	5%

Comparison of baseline characteristics from KEYNOTE-407, SEER and NCLA (Updated for correct median age and % male)

	KEYNOTE-407 [24]	SEER [25]	NCLA [17]
Median age	65	70	72[26]
% Male	78.3%	65% (2010-14)	58%[26]

B23. Priority question: In the submitted model, on worksheet "SEER Data" column J, the model accounts for the OS benefit of pembrolizumab by applying a relative risk derived from months 7-12 in KEYNOTE-407 to the annual SEER data. Please comment on the potential selection bias associated with applying a relative risk derived from an interval part-way through the follow-up period.

It was deemed inappropriate to base the relative risk on data from closer to the end-point of the trial follow up period (month 13-18) as data on events were too sparse. Inclusion of data from the early portion of the trial for OS for deriving the relative risk would be adding weight to mortality during the period immediately following treatment initiation (when mortality risks are known to be very high) and most likely not reflective of the whole trial follow up period.

B24. CS section B.3.3.1 page 139 describes methods for modelling OS and PFS, but does not mention the selected modelling approach for PFS. Please explain how a 26-week cut-point and log normal model were selected for PFS.

The CS refers to appendix L where the following information can be found in pages 307-318.

B25. In CS section B.3.3.1 on page 139 and in the model please provide the actual SEER data used in the model, including information relating to:

(a) The defined patient population and inclusion criteria applied.

As mentioned on page 139 of the CS, as patients within the KEYNOTE-407 trial were an average of 2 months from their date of diagnosis with metastatic squamous NSCLC at baseline, survival within the SEER database was similarly analysed

starting from 2 months post-diagnosis. Patients were matched based on their tumour site and sub-type (NSCLC), stage (IV), histology (squamous).

(b) The relevant years for the included dataset.

As mentioned on page 139 of the CS, Data from 1992-2014 were analysed for metastatic squamous NSCLC patients. SEER data from 2010-2014 were utilised to assess survival during years 1-5 of follow-up, data from 2000-2014 for years 6-10 of follow-up and data from 1992-2014 for years 11-13 of follow-up. Beyond 13 years, there was insufficient sample size within SEER for stable reporting of estimates.

(c) How many patients were included?

The following numbers of patients were included in each analysis (number contributing any survival data over the course of the analysis):

- Years 1-5: 14,722
- Years 6-10: 27,366
- Years 11-13: 20,986

(d) Whether the probabilities are conditional "within-year" probabilities of survival, or cumulative probabilities of survival.

The SEER data output reflects cumulative probabilities of survival. The data were converted to conditional probabilities (annual risks of mortality) for use within the model.

B26. In CS appendices N page 350, with respect to the analysis of time-on-treatment data from KEYNOTE-407:

(a) Please clarify how the time on treatment data were analysed – are deaths counted as discontinuation events, or as censored observations? If deaths have been censored, please provide the time on treatment curve including deaths as events.

Deaths are discontinuation events if the patient was still on treatment at the time.

(b) Please clarify why a piecewise approach has not been used to model time on treatment for the pembrolizumab plus chemotherapy group.

The duration of extrapolation (2 years maximum) for ToT is much shorter than for OS/PFS and a one-piece model appears to provide a reasonable fit visually. Therefore for simplicity, two-piece modeling was not conducted.

(c) Was plausibility considered in the curve selection process?

Inputs and results were reviewed by 2 external health economists and 2 clinical oncologists, there was no obviously implausible result – treatment was stopped at 2 years.

B27. In CS appendices L page 325, it states that "Two scenarios were implemented in the model to estimate OS and PFS for the indirect comparison:1) Based on constant hazard ratios (HRs), and 2) With time-varying HRs" for indirect comparison to pembrolizumab monotherapy. However, in the CS the time-varying HRs analysis was not presented. Please clarify what indirect treatment comparison analysis was performed when comparing pembrolizumab combination with pembrolizumab monotherapy? Please can you also clarify what model was used to extrapolate OS and PFS for the PD-L1 strong expression patients, and what HRs were used?

The constant hazard ratio was used when comparing pembrolizumab combination to pembrolizumab monotherapy. The OS extrapolation for pembrolizumab combination was as per the base case – using SEER data and the extrapolation of PFS was also as the base case, using a cut point of week 26 and a log-normal parametric extrapolation. Based on the indirect treatment comparison, in the sub-group with PD-L1 ≥ 50%, the hazard ratio for mortality for pembrolizumab monotherapy vs. pembrolizumab + chemotherapy (1.03, 95% CI 0.53-2.00) is not statistically different between comparators.

B28. Priority question: Please perform the extrapolation using the entire Kaplan-Meier data for OS and PFS for the two arms in KEYNOTE-407 (ITT and PD-L1 <1%, 1-49% and ≥50% subgroups) (first mentioned - section B.1.1 table 1 page 15). Please consider the use of more flexible models such as Royston and Parmar spline models in the case when the empirical hazard has a complex form.

Use of the full KM curve for extrapolation informed by SEER population data is not appropriate for the reasons described previously related to sparse data at the tail of the curve. The parametric extrapolation approach is not likely to produce a valid

long-term extrapolation. Inclusion of data from the early portion of the trial for OS for parametric extrapolation (i.e. prior to week 19) would be adding even further weight to mortality during the period immediately following treatment initiation (when mortality risks are known to be very high) and would not provide further insight into the potential for longer term remission/cure, which leads to discrepant results between the parametric extrapolation approach and that informed by SEER NSCLC population-based mortality risks. Also, the submitted CE model allows for the selection of a week 0 cut-point for OS, which would largely provide the requested results however MSD would not advocate this.

Adverse events

B29. In CS section B.3.4.4 page 161, please clarify the proportion of AEs which occurred more than once, if available. Please also clarify how the value of [redacted] days of duration across grade 3+ AEs was calculated.

Incidence (counts and percentages) of subjects who experienced more than 1 grade 3 to 5 specific preferred term of adverse events is reported in the Table below. There was a pooled mean duration of all cause grade 3-5 AEs of [redacted] in weeks. This was multiplied by 7 to come to a mean duration of [redacted] days.

Subjects With Grade 3-5 Adverse Events by Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
Subpopulation of Subjects with More Than 1 Specific Grade 3-5 AE (ASaT Population)

	Pembro Combo		Control	
	n	(%)	n	(%)
Subjects in population	[redacted]	[redacted]	[redacted]	[redacted]
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Anaphylactic reaction	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]

Atrial flutter	[redacted]	[redacted]	[redacted]	[redacted]
Autoimmune hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Clostridium difficile colitis	[redacted]	[redacted]	[redacted]	[redacted]
Duodenitis	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia klebsiella	[redacted]	[redacted]	[redacted]	[redacted]

Subjects With Grade 3-5 Adverse Events by Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
Subpopulation of Subjects with More Than 1 Specific Grade 3-5 AE (ASaT Population)

	Pembro Combo		Control	
	n	(%)	n	(%)
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
For subjects who crossed over to pembrolizumab from the Control Group, adverse events that occurred after the first dose of crossover phase are excluded.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA 20.1 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 03APR2018

Executable model

B30. In the submitted Model on worksheet “Lifetable UK”, please clarify;

(a) What the calculations in column W are intended to do? Note that sex-specific weights have already been applied.

The formula does not appear to double weight by sex, as it draws data from the original male-specific and female-specific population mortality risks to estimate a weighted probability of death per year, rather than General Population (post-weighted survival probability in Column V).

(b) The values in column X have been pasted as values – please provide the calculations used to generate these.

Column X has been updated with formula in the updated model.

(c) The sex-specific weights are applied in wrong year e.g. age 65 gets age 0 weight. Please correct this.

Apologies this has been corrected in the updated model.

(d) The general population mortality constraint overrides the modelled mortality rate for the intervention group after approximately 18 years. This implicitly assumes that ~9.9% of patients are cured. Please comment on the plausibility of this assumption.

If the question is understood correctly, >9.9% of patients annually must have died within the general population around year 18, for that to have over-ridden the SEER extrapolated risk. This can be considered plausible, as the general population risks account for increasing mortality with age, whereas for SEER there was not enough data to model mortality precisely beyond year 13 and therefore the constant 9.9% risk is a valid assumption.

B31. Priority question: In the submitted model, on worksheet "NMA-ITC OS (conHR)" column AK we believe that there is an error in the calculation of the OS function for the NMA comparators. The formulae in column AK appear to use the Kaplan-Meier function followed by an exponential extrapolation. This cumulative OS

function is then raised to the power of the hazard ratio from the NMA to estimate the survivor function for the comparator. However, we believe that you intended to apply the same baseline function as the "within-trial" comparison against standard care i.e. the Kaplan-Meier function followed by risks from SEER. Please confirm that this is an error; if it is not, please explain the logic of this approach.

The data in column AK, and on the worksheet generally, only reflect implementation of the parametric extrapolation approach for the indirect comparators.
The SEER-based approach is implemented for the indirect treatment comparators on the 'Modeled OS' worksheet in the formulae in columns Y to AA. Therefore there is not an error.

Resource use and costs

B32. In the submitted model, what duration of therapy was assumed for immunotherapies for patients who received second-line pembrolizumab monotherapy after progression in KEYNOTE-407?

The duration of 2L immunotherapies in the chemotherapy arm is reported in cells D147 and D150 on the Regimen Costs worksheet which is 10.7 cycles for those who had only received anti-PD1/PD-L1 therapy and 14.6 for those who had both an anti-PD1/PD-L1 therapy and chemotherapy sequentially following 1L therapy.

B33. What is assumed about relative dose intensity in the economic comparisons based on the NMA analyses (first mentioned – section B.2.9.1 page 80)?

Dose intensity for the comparators derived from the NMA analysis is assumed equivalent to that of the KEYNOTE-407 trial comparator arm in the economic analysis ([redacted]%).

B34. Priority question: In CS section B.3.5.7 page 177, the model uses post-progression treatment probabilities based on interim analysis 2 (at a point whereby [redacted] patients have progressed). Please comment on whether these probabilities are likely to be higher in the final data cut.

With regards to post-discontinuation treatment probabilities (mentioned on the page 177 highlighted), the percentage of trial patients receiving a subsequent treatment may increase with additional follow-up, although the degree of possible increase is

unknown. If anything, there would likely be a more favourable impact for the Pembrolizumab combination ICER, as 2L+ treatments used are less expensive than for the SoC arm (where there was extensive PD-L1/PD-1 use).

B35. In CS section 3.2.3 Table 56 page 134 it states that Personal Social Services (PSS) costs were not included in the analysis, yet the CS later goes on to describe the costs of community nurse visits. Please clarify this discrepancy. In addition, please highlight if other specific PSS costs are believed to have been excluded from the model?

Community nursing was identified through the resource use and cost economic literature review as a cost which had been included for previous economic evaluations in this patient population. Therefore in order to try to include all relevant costs from those identified in the SLR, it was included. It is also possible that this type of nursing care is funded by the NHS.

B36. In CS section B.3.5.7 page 177, it states: "Within the model, 2L IO therapy following pembrolizumab combination or monotherapy has not been included as this would not represent UK clinical practice". Please clarify;

(a) How many patients in KEYNOTE-407 does this correspond to?

Four patients.

(b) How many patients received second-line immunotherapy using pembrolizumab and how many received nivolumab?

Four patients in the pembrolizumab combination arm received 2L IO therapy – 2 nivolumab, 1 pembrolizumab and 1 atezolizumab. For the pembrolizumab monotherapy arm, 2 patients received nivolumab.

(c) Did any patients receive atezolizumab?

Yes – 1 patient as mentioned in (c)

(d) In Table 84, does the second data row (pembrolizumab [200mg] – [redacted]) relate only to monotherapy?

Yes, it is the proportion of SoC patients who went on to 2L pembrolizumab monotherapy.

Section C: Textual clarification and additional points

C1. In CS section B.3.3.1 page 138, it states "It can be assumed then that in addition to 4 cycles of 1L platinum chemotherapy available as the 1L SoC for these patients would bring this to around 19 months." Please clarify the logic underpinning this statement. Please also provide a clear reference for the value of 16.01 months.

The value should be 16.06 and is from the ERG report (Table 9) of the NICE TA 483 – Nivolumab for previously treated squamous non-small-cell lung cancer. Four cycles of platinum chemotherapy at a dose of 3QW would equate to 3 months treatment in a 1L setting for a patient to then reach 2L therapy for which the preferred assumptions in the TA mentioned was a OS of 16.06 months, bringing 1L and 2L SoC current survival estimated at around 19 months according to the committee preferred assumptions in this TA.

C2. In CS section B.3.3.1 Table 65 page 147, it states that 36.4% of patients in KEYNOTE-407 were male. However, Table 7 reports that 81.4% of patients in this trial were male. Please clarify which proportion is correct.

The table should read 78.3% and the reference should be the MSD subject disposition report provided in the original reference pack as this is based on the European subject ITT population. The value in Table 7 (81.4%) is the overall population value rather than European subjects.

C3. In CS section B.3.3.1 Table 65 page 147, it states that the median age of patients in KEYNOTE-407 was 75. However, Table 7 reports that the median age of patients in this trial was 65. Please clarify which median age is correct.

Apologies, 75 is a typo. 65 is the correct European subject mean age.

C4. In CS section B.3.3.1 page 145, it states "To extrapolate the PFS and OS (in scenario analysis) from KEYNOTE-407, to populate the area-under-the-curve (AUC) partitioned survival approach, guidance from the NICE DSU was followed to identify base case parametric survival models for OS and PFS" Please clarify if this

statement is referring to the base case or the scenario analysis (both are mentioned).

For the base case analysis using SEER data for extrapolation of OS, NICE DSU was not used. For the parametric extrapolations of PFS and OS (within the relevant scenario analysis and PFS in the base case) beyond the trial were carried out in line with NICE DSU guidelines.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]

Additional Clarification Questions

December 2018

File name	Version	Contains confidential information	Date
ID1306 pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer	**Final**	**Yes**	**10/12/2018**

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.

Clarification regarding executable model

Additional clarification regarding question B31

Priority question 1. We have concerns that the company's response to question B31 of the clarification letter is not correct.

To illustrate this issue, please set the Hazard Ratios (HRs) equal to 1.0 in the worksheet "NMA-ITC OS (conHR)" (cells O19:O21) and then look at the Life Years Gained (LYG) in the worksheet "Results" (cells H7:K7). We believe that doing this should produce a result whereby the predicted LYG for the Network Meta-Analysis (NMA) comparators are the same as those for the pembrolizumab combination therapy. However, this is not the case – instead, the model suggests that the NMA comparators produce >1 Quality Adjusted Life Years (QALYs) more than pembrolizumab combination therapy. We suspect that the model is subject to errors due to two issues:

(a) The baseline pembrolizumab combination Overall Survival (OS) curve to which the HR is applied in the model is the Kaplan-Meier + exponential function, not the Kaplan-Meier + SEER model.

(b) Given that the HRs from the NMA are intended to be applied to the pembrolizumab combination therapy OS curve, there appears to be a further error in worksheet “Modeled OS” whereby the columns which estimate OS functions for the NMA comparators (columns Y, Z and AA) are using the "trial chemotherapy" OS function (column W) rather than the pembrolizumab combination therapy OS function (column V).

Please investigate these issues further. If you agree that these are errors, please provide a corrected version of the model. If not, please provide a clear explanation regarding these issues.

The initial formula introduced had aimed to relate SEER-based trajectories for OS for the chemotherapy arm to those for indirect comparators however this may not have been robust enough. The formulae in columns Y, Z and AA of the Modeled OS worksheet and the Life Years for Pembrolizumab + Chemotherapy and each indirect treatment comparator have been updated and now are equal when the NMA-ITC OS HRs are set to 1.0 for each indirect treatment comparator.

Additional clarification regarding pembrolizumab monotherapy Indirect Treatment Comparison

Priority question 2. The model uses an HR for pembrolizumab monotherapy versus combination therapy of [redacted] (in worksheet "NMA-ITC OS (conHR)" cell O18). In the model, this leads to pembrolizumab monotherapy producing more LYGs than pembrolizumab combination therapy. However, in the company submission on page 99, it states that the HR for pembrolizumab combination versus monotherapy is 0.97; this would suggest that monotherapy is less effective than combination therapy. Similarly,

[redacted]

Please investigate this issue. If you agree that this is an error, please provide a corrected version of the model. If not, please provide a clear explanation regarding why the model produces this counter-intuitive result.

Apologies, a previous estimate was carried forward into the model and the ERG are correct, the value should be the inverse of [redacted] as per page 99 and the

appendix of the company submission suggested. The model has been updated for this also and uploaded with this response.

NICE National Institute for Health and Care Excellence

Patient organisation submission – Roy Castle Lung Cancer Foundation

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]

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

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you 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, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity). 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 metastatic squamous Non Small Cell Lung Cancer (NSCLC).
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and	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.

carers to include in your submission?	
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?	A diagnosis of metastatic squamous NSCLC is devastating. Squamous accounts for around 20 to 30% of NSCLC and is generally associated with a shorter survival than non-squamous.. The outlook for this patient group is particularly poor. with an obvious impact on family and carers. Patients tend to be symptomatic, often with symptoms such as breathlessness, cough and weight loss – all of which can be 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?	Having metastatic disease at diagnosis, there are currently no potentially curative therapy options for this group of patients. For some patients whose tumours express PD-L1 at or above 50%, initial treatment can be with the immunotherapy agent, Pembrolizumab (alone). This is, in general well tolerated and represents a welcome recent advance in the treatment of this patient group. For the patient group, in which tumours express PD-L1 below 50%, however, first line systemic therapy is with traditional platinum based doublet chemotherapy, with the well established associated side effect profile. For the latter group in particular, outcomes remain poor.

8. Is there an unmet need for patients with this condition?	Most definitely. This patient population has not benefited from the improvements in outcome, which we have seen in the introduction of Target therapies in NSCLC (EGFR, ALK, ROS- 1)
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	From the KEYNOTE- 407 study, published in the NEJM, benefit is seen by patients in the improvement observed in overall survival – 11.3 months in the chemotherapy only arm, increasing to 15.9 months when Pembrolizumab is added. Also, median Progression Free Survival was 6.4 months in the Pembrolizumab/chemotherapy arm and 4.8 months in the chemotherapy/placebo arm. The potential for extensions in life, is of paramount importance to this patient population and their families. Importantly, the benefit in overall survival was seen across differing levels of PD-L1 expression.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The additive side effects of receiving Immunotherapy and chemotherapy together.

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?	

NICE National Institute for Health and Care Excellence

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • Massive unmet need in this patient population • Research has shown improvement in overall survival and progression free survival, with this new combination, as compared with chemotherapy alone • Improvement seen across different levels of PD-L1

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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

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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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	BTOG-NCRI-ACP-RCP-RCR

3. Job title or position	RCP registrar
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**BTOG-NCRI-ACP-RCP-RCR**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**None**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	This is for advanced lung cancer (NSCLC). Aim of treatment is to improve quality of life, prevent progression and improve survival

or prevent progression or disability.)	
7. 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 benefit is usually noticed when there is reduction radiologically by 25%. Generally patients want to see clinical improvement and survival advantage. Lack of progression is also meaningful as this usually corresponds with deterioration in QOL.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Currently chemotherapy or immunotherapy available first line See below
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Currently first line treatment would be with chemotherapy. If PDL1 >50% patients receive pembrolizumab in the NHS. If <50% and >1% pembrolizumab is given second line (other checkpoint inhibitors: nivolumab and atezolizumab also available). There is treatment available, evidence suggests that combination of chemotherapy and immunotherapy better than chemotherapy alone.
• Are any clinical guidelines used in the	Yes: NICE being updated, ASCO/ESMO guidelines of treatment

treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well defined pathway due to commissioning of drugs in particular settings. Very little variation around the country with regards general lines of treatment.
• What impact would the technology have on the current pathway of care?	Would receive combination of chemotherapy and immunotherapy together. May actually save chemotherapy chair time episodes and treatment would not be given sequentially. Very little increase in toxicity with combination treatment.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Both drugs currently used separately so no new training or equipment will be required.
• How does healthcare resource use differ between the technology and current care?	Time in the chemotherapy chair will be longer but may reduce number of episodes for each patient as everything is given upfront and not an additional line of treatment.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No capacity issue as drugs already being given separately
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Keynote 407 (September 25, 2018 DOI: 10.1056/NEJMoa1810865) Presented at ASCO 2018. Randomised controlled study of carb/pacli/pembro vs carb/pacli/placebo. Median follow up of 7.8 months: median OS 15.9m vs 11.3m (HR=0.64 p<0.001) in favour of trio drug combo. This is meaningful and clinically significant difference
• Do you expect the technology to increase length of life more than current care?	Yes the primary end point for the trial was met ie. Overall survival. This is better that chemotherapy alone
• Do you expect the technology to increase health-related quality of life more than current care?	Yes The toxicity of the trio was no greater than with chemotherapy alone. Delaying progression and improving survival in itself will improve QOL. HRQOL were not reported specifically in this paper.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There may be patients >50% PDL1 expression who may benefit more with pembrolizumab alone as less toxic than chemo/pembro. Follow up is so short that it is difficult to know whether the PDL1 >50% will do just as well with pembro alone.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No extra tests or technology required

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Radiological RECIST criteria generally determines progression. Toxicity will also guide stopping treatment.
15. 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
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Needs more FU to determine whether all group benefit but currently all groups have statistically significant benefit over chemotherapy alone

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No additional treatment first line
• Does the use of the technology address any particular unmet need of the patient population?	None
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	None
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Carboplatin/paclitaxel is NOT SOC in UK. SOC in US and much of the Europe. Licensed treatment. Alopecia greater than SOC in UK (gem/carb or vin/carb)

• If not, how could the results be extrapolated to the UK setting?	Carb/pacl is very standard treatment option outside the UK. Licensed indication. The approval must be on this combination as per the evidence
• What, in your view, are the most important outcomes, and were they measured in the trials?	Primary endpoints were OS and PFS. Despite very early follow up at 7.8 months these were met.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Early FU and may have more toxicity outcomes following longer FU
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	This would be consistent with the pembrolizumab/chemotherapy combination data in non-squamous population of Keynote 189 which has PFS improvement only as yet and not reached median survival.

21. How do data on real-world experience compare with the trial data?	Patients in trials are always fitter and motivated, likely better PS. Combination outside context of trial population needs to be used with caution.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
22b. 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 submission.

- Overall survival difference seen at 7.8 months median FU, despite crossover in the chemotherapy only arm, suggesting earlier use of checkpoint inhibitors is a more successful strategy. OS 15.9m vs 11.3m (HR=0.64 p<0.001) in favour of trio regime
- Toxicity no worse than standard treatment
- SOC in the study NOT UK standard treatment for squamous NSCLC but licensed chemotherapy and widely accepted SOC in the world.
- Combination of chemotherapy and pembrolizumab may reduce number of chemotherapy attendance as this does not represent an extra line of treatment but combination of first and second line

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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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	[redacted]
2. Name of organisation	**NCRI/BTOG**

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):
5a. Brief description of the organisation (including who funds it).	National Cancer Research Institute (DOH) British Thoracic Oncology Group
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**None**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	This is for advanced lung cancer (NSCLC). Aim of treatment is to improve quality of life, prevent progression and improve survival

or prevent progression or disability.)	
7. 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 benefit is usually noticed when there is reduction radiologically by 25%. Generally patients want to see clinical improvement and survival advantage. Lack of progression is also meaningful as this usually corresponds with deterioration in QOL.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Currently chemotherapy or immunotherapy available first line See below
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Currently first line treatment would be with chemotherapy. If PDL1 >50% patients receive pembrolizumab in the NHS. If <50% and >1% pembrolizumab is given second line (other checkpoint inhibitors: nivolumab and atezolizumab also available). There is treatment available, evidence suggests that combination of chemotherapy and immunotherapy better than chemotherapy alone.
• Are any clinical guidelines used in the	Yes: NICE being updated, ASCO/ESMO guidelines of treatment

treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well defined pathway due to commissioning of drugs in particular settings. Very little variation around the country with regards general lines of treatment.
• What impact would the technology have on the current pathway of care?	Would receive combination of chemotherapy and immunotherapy together. May actually save chemotherapy chair time episodes and treatment would not be given sequentially. Very little increase in toxicity with combination treatment.
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• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No capacity issue as drugs already being given separately
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Keynote 407 (September 25, 2018 DOI: 10.1056/NEJMoa1810865) Presented at ASCO 2018. Randomised controlled study of carb/pacli/pembro vs carb/pacli/placebo. Median follow up of 7.8 months: median OS 15.9m vs 11.3m (HR=0.64 p<0.001) in favour of trio drug combo. This is meaningful and clinically significant difference
• Do you expect the technology to increase length of life more than current care?	Yes the primary end point for the trial was met ie. Overall survival. This is better than chemotherapy alone
• Do you expect the technology to increase health-related quality of life more than current care?	Yes The toxicity of the trio was no greater than with chemotherapy alone. Delaying progression and improving survival in itself will improve QOL. HRQOL were not reported specifically in this paper.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There may be patients >50% PDL1 expression who may benefit more with pembrolizumab alone as less toxic than chemo/pembro. Follow up is so short that it is difficult to know whether the PDL1 >50% will do just as well with pembro alone.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No extra tests or technology required

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Radiological RECIST criteria generally determines progression. Toxicity will also guide stopping treatment.
15. 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
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Needs more FU to determine whether all group benefit but currently all groups have statistically significant benefit over chemotherapy alone

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No additional treatment first line
• Does the use of the technology address any particular unmet need of the patient population?	None
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	None
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Carboplatin/paclitaxel is NOT SOC in UK. SOC in US and much of the Europe. Licensed treatment. Alopecia greater than SOC in UK (gem/carb or vin/carb)

• If not, how could the results be extrapolated to the UK setting?	Carb/pacl is very standard treatment option outside the UK. Licensed indication. The approval must be on this combination as per the evidence
• What, in your view, are the most important outcomes, and were they measured in the trials?	Primary endpoints were OS and PFS. Despite very early follow up at 7.8 months these were met.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Early FU and may have more toxicity outcomes following longer FU
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	This would be consistent with the pembrolizumab/chemotherapy combination data in non-squamous population of Keynote 189 which has PFS improvement only as yet and not reached median survival.

21. How do data on real-world experience compare with the trial data?	Patients in trials are always fitter and motivated, likely better PS. Combination outside context of trial population needs to be used with caution.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
22b. 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 submission.

- Overall survival difference seen at 7.8 months median FU, despite crossover in the chemotherapy only arm, suggesting earlier use of checkpoint inhibitors is a more successful strategy. OS 15.9m vs 11.3m (HR=0.64 p<0.001) in favour of trio regime
- Toxicity no worse than standard treatment with chemotherapy
- SOC in the study NOT UK standard treatment for squamous NSCLC but licensed chemotherapy and widely accepted SOC in the world.
- Combination of chemotherapy and pembrolizumab may reduce number of chemotherapy attendance as this does not represent an extra line of treatment but combination of first and second line

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]

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.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you 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 13 pages.

About you	
1. Your name	**Alastair Greystoke**
2. Name of organisation	**Newcastle upon Tyne Hospitals NHS Foundation Trust**

3. Job title or position	**Senior Lecturer**
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.)	Palliate cancer related symptoms, shrink down cancer on radiological imaging and prevent progression as long as possible 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.)	An improvement in Progression free survival of more than 3 months, an improvement in radiological response rates by 10 % an improvement in overall survival by more than 6 weeks, or an improvement in survival at 5 years of more than 3%.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are no licensed targeted therapies in Squamous Lung Cancer. Response rates and progression free survival with platinum doublet chemotherapy are limited. Most patients will get limited response and disease control with single agent immunotherapy. The role of biomarkers to predict patients most likely to respond to immunotherapy such as PDL1 are less well established in squamous lung cancer than in non-squamous lung cancer.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Patients with tumours with PDL1 score <50% and performance status 0-1 (and some patients with performance status 2) may be offered platinum doublet chemotherapy. Most UK centres use carboplatin and gemcitabine but other partners can be used apart from gemcitabine such as vinorelbine and paclitaxel. On progression in patients with PS0-1 treatment may be offered with single agent with immunotherapy which may be nivolumab, atezolizumab or pembrolizumab (PDL1 +ve tumours only for pembrolizumab) until progression. Patients who progress or who are not suitable for immunotherapy 2nd line may be offered docetaxel but rates of using this in squamous NSCLC in the UK are low. In patients with tumours expressing PDL1>50% and PS0-1 pembrolizumab may be offered in the 1st line setting; with platinum doublet chemotherapy used on progression.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guideline CG121is in place but is in the process of being updated to take account of the rapid changes in the treatment of lung cancer. The recently updated ESMO guideline is used by some clinicians ESMO clinical guidelines as to management of metastatic lung cancer Planchard et al. ESMO NSCLC Guidelines 2018 Ann Oncol (2018) 29 (suppl 4): iv192–iv237. NICE technology appraisals TA531, TA428, TA483,TA520
• 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 of care is relatively well defined. There may be differences in the platinum doublet chemotherapy used as described above. There may be differences in the immunotherapy used between nivolumab, atezolizumab or pembrolizumab as described above
• What impact would the technology have on the current pathway of care?	In patients with PS0-1 and no contraindications to immunotherapy the 1st treatment offered would be chemotherapy and immunotherapy combined with carboplatin, paclitaxel and pembrolizumab. On

	progression the treatment options would be limited with some patients offered docetaxel but many moving to active symptom control at that point.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	There will be slight differences in treatment administration discussed below. The toxicity seems to be similar to what might be expected from chemotherapy and immunotherapy given by themselves with no additive toxicity seen. Treatment algorithms are already in place for both chemotherapy and immunotherapy toxicity.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist tertiary cancer centres with experience in delivering both chemotherapy and immunotherapy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No extra investment envisaged
12. Do you expect the technology to provide clinically	

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes. Whilst the survival curves are relatively immature the early pronounced separation with already a statistical difference suggests that this treatment may be associated with long term survival benefit, and this has been seen with other chemotherapy immunotherapy studies such as in non squamous NSCLC. The separation in survival curves actually appears more pronounced than observed at a similar stage in the studies n Non squamous NSCLC.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. In general lung cancer patients health related quality of life is driven by tumour related symptoms. Given the high tumour response rates seen with this combination it is likely that quality of life will improve. The toxicity profile appears to be reasonable (see question 11) and in general is unlikely to have a major impact on quality of life in most patients although there may be some patients who experience severe toxicity.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
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 may be more difficult to administer for healthcare professionals. When patients receive both chemotherapy and immunotherapy and present acutely it can be more difficult to determine whether symptoms are related to chemotherapy, immunotherapy or the underlying disease. However chemotherapy and immunotherapy combinations are now recommended in non squamous NSCLC and clinicians should be developing experience in the assessment and management of toxicities of chemotherapy and immunotherapy combinations.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing should be required; PDL1 testing at 1st diagnosis is becoming well established in the NHS. Patients will be monitored as previously with oncologist/ specialist nurse review to ensure clinical benefit and tolerability with regular CT scans to document formal response to treatment as with present care.
16. Do you consider that the use of the technology will result in any substantial health-	No

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
• Is the technology a 'step-change' in the management of the condition?	Yes. This is the 1st time we have seen data using chemotherapy and immunotherapy in combination for squamous NSCLC. The anticipated improvements in response, progression free and overall survival if translated from the clinical trials to the real world will be a "step-change".
• Does the use of the technology address any particular unmet need of the patient population?	No

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?	Using chemotherapy and immunotherapy can both result in the side-effects that are well established with these agents (For chemotherapy mainly nausea, myelosuppression and mucosal barrier disruptions; for immunotherapy the auto-immune side-effects). There does not appear to be any additive effects. Management of both chemotherapy and immunotherapy are well-established. In patients that get severe adverse effects that can cause a major impact on quality of life which can be long lasting
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, although restricted to Performance Status 0-1 which will represent only a proportion of patients.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival Quality of Life Progression Free Survival Response rate

	These were captured within the clinical trial, although data as to overall survival is still maturing
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	We do not yet have any real world data in this setting. The chemotherapy and immunotherapy combination in the non-squamous cancer setting is just beginning to accumulate and we do not yet know if it will match the data seen in clinical trials

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23.	• Question 10 – how much more time would be needed to administer pembrolizumab in combination to people with NSCLC compared to current SOC and to what extend is this potentially offset by less episodes? The Paclitaxel takes approximately 3 hours to give, along with the 30-60 minutes for the pembrolizumab. This compares to 30 minutes administration time for gemcitabine. However this will be offset to some extent by not having to attend for the day 8 gemcitabine. Although this only removes another 30 minutes of administration time there is additional time saved for the nurse who will have to reassess the patient and blood tests prior to administration.

	• Question 18 – You have stated that the comparator in the pivotal trial is not SOC in the U.K. How much difference would having the U.K SOC as a comparator have to trail results? Do you envisage significant differences in progression free survival and overall survival if the U.K SOC was used? I do not envisage any major difference between the comparator carboplatin-pacliatxel and UK SoC Carboplatin-gemcitabine. There was a meta-analysis that showed no major differences between the various treatment regimens used (Treat et al Lung Cancer, 2012; 76 (2), 222–227)

Key messages

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

- Carboplatin-paclitaxel and pembrolizumab is associated with higher response rates, progression free and over all survival than chemotherapy alone.
- This may be at the cost of some additional toxicity but chemotherapy immunotherapy combinations in place for non-squamous NSCLC and management algorithms should be in place.
- The chemotherapy backbone is different that commonly used in the UK, but that should have no major impact on the effectiveness analysis
- There will be some differences in side-effects and administration time in using the different chemotherapy backbone.

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Cancer Drugs Fund Clinical Lead statement

Pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel for the 1st line treatment of metastatic squamous non small cell lung cancer [ID1306]

Background

1. The treatment pathway for non small cell lung cancer (NSCLC) and for the squamous (S) variety (25-30% of all NSCLC) is currently changing rapidly and has the potential to change even more in the near future as immunotherapy both moves to earlier lines of treatment in the treatment pathway and is combined with other treatments.

2. The marketing authorisation (MA) for pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel is likely to be in patients with metastatic S NSCLC as 1st line systemic treatment in patients and regardless of PD-L1 expression.

Treatment pathway and comparators - immunotherapy

3. The one current 1st line NICE routinely recommended immunotherapy for metastatic S NSCLC is pembrolizumab monotherapy in those patients with a PD-L1 tumour proportion score (TPS) of 50-100%. There is a 2 year stopping rule for this treatment. In such patients, standard 2nd line treatment is then with the displaced '1st line' cytotoxic combination chemotherapy ie the treatment pathway has shifted along with the insertion of pembrolizumab as 1st line systemic therapy. Patients treated with

1st line pembrolizumab would not be eligible for re-treatment with further immunotherapy.

4. For patients previously treated with 1st line cytotoxic combination chemotherapy, pembrolizumab monotherapy is NICE-recommended for routine commissioning in S NSCLC in patients with locally advanced/metastatic disease who have had previous platinum-based chemotherapy. There is a 2 year stopping rule in operation for pembrolizumab in this indication and this NICE recommendation applies only to those patients with PD-L1 expression of ≥1%. Atezolizumab monotherapy is also recommended in this same indication in S NSCLC except that patients can have a PD-L1 expression of 0-100%. Atezolizumab in this indication also has a 2 year stopping rule.

5. Since the approval of atezolizumab monotherapy in patients previously treated with chemotherapy, atezolizumab has largely displaced use of pembrolizumab in this 2nd line indication. The ratio of patients treated with 2nd line atezolizumab to 2nd line pembrolizumab is currently approaching about 3 to 1. Although the MA for pembrolizumab now allows treatment every 6 weeks, feedback to NHS England considers that most NSCLC patients will remain on 3 weekly cycles of immunotherapy given the need for frequent monitoring as a consequence of both the nature of lung cancer and the frequent comorbidities seen in NSCLC patients. Thus the main 2nd line immunotherapy choice in S NSCLC is atezolizumab.

Treatment pathway – cytotoxic chemotherapy

6. A number of chemotherapy options are recommended by NICE as 1st line cytotoxic chemotherapy in S NSCLC. By far the most commonly used regimen in England is carboplatin plus gemcitabine. Carboplatin in combination with vinorelbine is used in

a minority of cases. Carboplatin in combination with a taxane (paclitaxel, docetaxel) is very rarely used as 1st line therapy (mainly because it causes hair loss whereas carboplatin/gemcitabine and carboplatin/vinorelbine generally do not).

7. Carboplatin is generally used at a dose determined in the Calvert formula and at an area under the concentration versus time curve (AUC) of AUC 4-5.

8. If further cytotoxic chemotherapy is used at all, docetaxel is the main cytotoxic agent used on failure of platinum-based chemotherapy in S NSCLC.

9. Nab-paclitaxel is licensed in the 1st line cytotoxic treatment of NSCLC but is not commissioned by NHS England as Celgene failed to make a submission when invited by NICE to do so (TA362). TA362 was therefore terminated by NICE. NHS England does not therefore regard the consideration of pembrolizumab plus carboplatin and nab-paclitaxel as being relevant in this appraisal.

Comparators – current treatment pathway

10. The correct comparator for pembrolizumab in combination with carboplatin plus paclitaxel in the 1st line metastatic S NSCLC PD-L1 TPS 0-49% population is thus platinum-based chemotherapy in the form of carboplatin plus gemcitabine or carboplatin plus vinorelbine. The sequence of treatments to be compared would be 1st line pembrolizumab in combination with carboplatin plus paclitaxel and then 2nd line docetaxel at relapse versus 1st line carboplatin plus gemcitabine or 1st line carboplatin plus vinorelbine and then 2nd line atezolizumab (PD-L1 0-100%) or 2nd line pembrolizumab (PD-L1 1-100%) and then 3rd line docetaxel.

11. The correct comparator for pembrolizumab in combination with carboplatin plus paclitaxel in the 1st line metastatic S NSCLC PD-L1 TPS 50-100% population is thus pembrolizumab monotherapy. The sequence of treatments to be compared would be 1st line pembrolizumab in combination with carboplatin plus paclitaxel and then 2nd line docetaxel at relapse versus 1st line pembrolizumab and then 2nd line carboplatin plus gemcitabine or 2nd line carboplatin plus vinorelbine and then 3rd line docetaxel.

Metastatic S NSCLC with a PD-L1 TPS 0-49%

12. There would be significant clinical and patient interest in the use of pembrolizumab in combination with carboplatin and paclitaxel in this 1st line population as it allows use of immunotherapy 1st line in a population of patients who can currently only access immunotherapy 2nd line. Patients fit enough for immunotherapy would not choose to wait to have immunotherapy 2nd line as the attrition rates from NSCLC 1st line to 2nd line systemic therapy is high (approximately 50% of 1st line patients do not proceed to further systemic therapy).

13. Clinicians rarely use the combination of carboplatin plus paclitaxel in S NSCLC. The Keynote 046 trial used a higher dose of carboplatin than is considered usual in England (AUC 6 rather than AUC 4-5) and used the 3-weekly schedule of paclitaxel at a dose of 200mg/m². There will be unfamiliarity with both this combination and the dosage of carboplatin in this population of S NSCLC patients.

Metastatic S NSCLC with a PD-L1 TPS of 50-100%

14. The metastatic S NSCLC population with a PD-L1 TPS of 50-100% is currently treated with pembrolizumab monotherapy. How many of such patients when faced with the choice of

pembrolizumab monotherapy or pembrolizumab in combination with carboplatin plus (hair-losing) paclitaxel will choose the latter is debateable. NHS England considers that many patients will elect to receive pembrolizumab monotherapy in order to avoid the additional toxicity of combination chemotherapy.

Commissioning issues

15. In terms of assessment of pembrolizumb in combination with carboplatin and paclitaxel versus the correct comparator for the above 2 patient groups in this appraisal, the use of this combination will result in a significantly increased use of chair time for patients in chemotherapy units. This is because paclitaxel requires a pre-medication to be given in advance of treatment and is administered as a 3 hour infusion time. Gemcitabine or vinorelbine are administered over much shorter treatment durations as is pembrolizumab monotherapy.

Comment on clinical trial data.

16. The median duration of follow-up in Keynote 047 was only 7.8 months which therefore represents a very immature dataset. Few patients are at risk in the survival analysis after 12 months. NHS England notes that the final trial analysis is due in [redacted].

17. The current short nature of follow up in Keynote 047 also means that there is uncertainty as to the longer term immune-related toxicities of this combination.

Specific issues for this technology appraisal

18. NHS England notes that the indirect treatment comparison between pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy in the PD-L1 TPS 50-100% group showed similar outcomes for efficacy. The confidence intervals in

this comparison are very wide. There is however no doubt in the increased toxicity which would be seen in those patients treated with the combination of pembrolizumab and chemotherapy.

19. NHS England notes the modelling of survival in the comparator arm in the PD-L1 0-49% group and considers this pessimistic given MSD's previous assumptions when presenting its case for 2nd line pembrolizumab in the PD-L1 1-100% population and also because of the long term Keynote 010 data in the PD-L1 1-100% population. Using historical data from the pre-immunotherapy era for the comparator chemotherapy group in the PD-L1 0-49% analysis is flawed.

20. MSD has modelled a life time treatment effect for pembrolizumab in combination with chemotherapy despite many previous appraisals at NICE opting for consideration of 3 and 5 year treatment effect durations when a 2 year cap in treatment duration is in operation.

Commissioning perspective

21. NHS England is aware that immunotherapy drugs as monotherapy or in combination with chemotherapy are recommended by NICE as 1st line therapy and as monotherapies after chemotherapy (pembrolizumab and atezolizumab are routinely commissioned; nivolumab is in the CDF). NHS England confirms that it does not commission the sequential use of any immunotherapy drugs in the NSCLC pathways. This is because of the lack of evidence of any sequential use and the biological plausibility argument of greatly reduced efficacy of a second immunotherapy drug after failure of a first immunotherapy drug.

22. If NICE recommends a treatment cap at 2 years, NHS England confirms its willing ness and determination to only commission a

maximum of a 2 year treatment duration of pembrolizumab in this indication, as it has already done so for all other immunotherapy options in NSCLC.

Generalisability to NHS practice

23. NHS England notes that the marketing authorisation may state that use of pembrolizumab in combination with carboplatin plus paclitaxel should be in patients with metastatic S NSCLC. The use of carboplatin in combination with gemcitabine or vinorelbine is used in patients with distantly metastatic (stage IV) and locally advanced stage IIIB disease S NSCLC. NHS England would wish to commission the use of this combination (if recommended by NICE) in patients with locally advanced or metastatic disease.

24. The Keynote 047 trial only allowed entry of patients with an ECOG performance score of 0 or 1. 29% of patients were of PS 0 which represents an impressive level of fitness for lung cancer patients. Restricting entry of just PS 0 or 1 patients into a clinical trial is reasonable given that pembrolizumab is being added to chemotherapy, one drug of which is being given at a higher dose than usual (carboplatin at a dose of AUC 6). NHS England would wish to commission use of pembrolizumab in combination with carboplatin plus paclitaxel in patients with a performance status of 0 or 1.

Implementing a positive NICE recommendation

NICE recognises that in the event of a positive recommendation, more prescriptive clinical commissioning criteria for treatments commissioned via Specialised Services will be implemented by NHS England to ensure appropriate use within the NHS.

NHS England is responsible for ensuring that the final clinical commissioning criteria are aligned with final guidance (section 1 – recommendation and section 3 – committee discussion).

Draft commissioning criteria

25. If pembrolizumab in combination with chemotherapy for treating advanced/metastatic S NSCLC is recommended for use within its marketing authorisation, NHS England proposes to use the following commissioning criteria:

- The patient must have histologically- or cytologically-confirmed S NSCLC which is locally advanced (stage IIIB) or distantly metastatic (stage IV) disease.
- The patient must have had testing for PD-L1
- The patient must not have received cytotoxic chemotherapy for his/her stage IIIB or stage IV disease. Patients who have received adjuvant chemotherapy, neoadjuvant chemotherapy or chemotherapy concurrent with radiotherapy for earlier stage disease are eligible for pembrolizumab in combination with carboplatin plus paclitaxelchemotherapy as long as there has been a treatment-free interval of at least 6 months from the last dose of chemotherapy
- The patient must have an ECOG performance score of 0 or 1
- The patient must commence cytotoxic chemotherapy at a dose of carboplatin calculated as being AUC 6 by the Calvert formula and paclitaxel at a dose of 200mg/m²
- The patient should receive a maximum of 4 cycles of carboplatin plus paclitaxel
- The patient should not have received any previous PD-1, PD-L1, PD-L2, anti CD137 agent or any checkpoint inhibitor
- The patient must not have any symptomatically active brain metastases or leptomeningeal disease

If this technology is recommended for routine commissioning in a subpopulation or with certain specifications (for example, a treatment continuation rule), the final commissioning criteria will reflect these conditions.

26. If pembrolizumab plus carboplatin and paclitaxel for treating advanced/metastatic S NSCLC is recommended for use in the Cancer Drugs Fund, the final commissioning criteria will reflect the patient eligibility criteria in the managed access agreement

Issues for discussion

27. All relevant issues for discussion have been raised above.

Issues for decision

28. All relevant issues for decision-making have been raised above.

Equality

29. No issues.

Author

Professor Peter Clark, NHS England National Clinical Lead for the Cancer Drugs Fund

April 2019

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer: A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	15th January 2019

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Declared competing interests of the authors

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

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Lesley Uttley and Alison Scope summarised and critiqued the clinical effectiveness evidence reported in the company's submission. Paul Tappenden and Aline Navega Biz critiqued the health economic analysis submitted by the company and undertook the ERG's exploratory analyses. Shijie Ren critiqued the statistical analyses presented in the company's submission. Mark Clowes critiqued the company's search strategy. Dennis Hadjiyiannakis, Gary Doherty and Laura Cove-Smith provided clinical expertise to the ERG and commented on the draft report. All authors were involved in drafting and revising the final report.

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Abbreviations

AE	Adverse event
AEOSI	Adverse event of special interest
AIC	Akaike Information Criterion
ALK	Anaplastic lymphoma kinase
ASaT	All-patients-as-treated
AUC	Area under the curve
BIC	Bayesian Information Criterion
BSA	Body surface area
CAA	Commercial Access Agreement
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CrI	Credible interval
CS	Company's submission
CSR	Clinical Study Report
CDF	Cancer Drugs Fund
DoR	Duration of response
DSA	Deterministic sensitivity analysis
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EoL	End of life
EORTC QLQ	European Organization for Research and Treatment of Cancer core quality of life questionnaire
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer quality of life questionnaire for lung cancer
ERG	Evidence Review Group
EQ-5D	Euroqol EQ-5D
EU	European Union
FAS	Full analysis set
FDA	US Food and Drug Administration
GP	General practitioner
HR	Hazard ratio
HRQoL	Health-related quality of life
IA2	Interim analysis two
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient-level data
IPTW	Inverse probability of treatment weighting
IRAE	Immune-related adverse event
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LSM	Least squares mean
LYG	Life year gained
Mg	Milligram
MSD	Merck Sharp & Dohme
MVN	Multivariate normal
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NIH	National Institutes of Health
NMA	Network meta-analyses
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient reported outcome measure
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
Q3W	Once every 3 weeks
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
RR	Relative risk
SAE	Serious adverse event
SC	Standard care
SD	Standard deviation
SE	Standard error
SEER	Surveillance Epidemiology and End Results
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SC	Standard care
STA	Single Technology Appraisal
TPS	Tumour proportion score
TTD	Time to treatment discontinuation
TTP	Time to progression
TTR	Time to response
US	United States
VAS	Visual analogue scale
WHO	World Health Organization

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The decision problem in the company submission is generally appropriate and is in line with the final NICE scope with regards to:

- Intervention - pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel (pembrolizumab combination therapy).
- Target population - adults with untreated, advanced (Stage IV) metastatic squamous non-small-cell lung cancer (NSCLC). The evidence included in the CS relates to patients who have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Pembrolizumab combination therapy does not currently hold a marketing authorisation for this indication; however, the CS is in line with the population included in the wording of the anticipated licence.
- Comparators - platinum-based combination chemotherapy regimens or pembrolizumab monotherapy (for people with tumours that express programmed death-ligand 1 [PD-L1] with a tumour proportion score [TPS] of at least 50%), as delivered in usual clinical practice.
- Outcomes - overall survival (OS), progression-free survival (PFS), time to response (TTR), duration of response (DoR), adverse events (AEs) and health-related quality of life (HRQoL).

As a consequence of uncertainty surrounding the currently available clinical evidence, the CS states that the company is seeking a Cancer Drugs Fund (CDF) recommendation for pembrolizumab combination therapy for the untreated metastatic squamous NSCLC population.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical evidence provided in the CS comprised the description of an ongoing, Phase 3, multi-centre trial (KEYNOTE-407) assessing the efficacy and safety of pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel versus placebo plus carboplatin and paclitaxel/nab-paclitaxel. A systematic literature review, including network meta-analyses (NMAs) and an indirect treatment comparison (ITC) analysis, was undertaken to compare pembrolizumab combination therapy with comparators including platinum-based combination chemotherapy regimens and pembrolizumab monotherapy. Separate analyses were conducted for the synthesis of OS and PFS evidence in two population groups: PD-L1 unselected and PD-L1 strong expression (TPS ≥50%).

Interim analysis 2 (IA2) of the 559 patients who entered the KEYNOTE-407 trial (data cut-off date 3rd April 2018) indicates that pembrolizumab combination therapy is statistically superior for OS, PFS and objective response rate (ORR – outcome not included in the NICE scope) compared with the control group. AEs occurring in KEYNOTE-407 were broadly in line with the known safety profiles of the two

treatment regimens. More immune-related adverse-events (IRAEs) and discontinuations occurred with pembrolizumab combination therapy than with control. The company's NMAs indicate that pembrolizumab combination therapy is an effective treatment relative to some of the chemotherapy regimens in the overall metastatic squamous NSCLC population (PD-L1 unselected). The company's ITC analysis within the PD-L1 TPS ≥50% subgroup suggests that pembrolizumab combination therapy is numerically superior to pembrolizumab monotherapy for both OS and PFS.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The Evidence Review Group (ERG) considers the KEYNOTE-407 trial to be high quality and relevant to the decision problem. Patients with strong PD-L1 expression did not receive first-line pembrolizumab monotherapy in this trial, as is standard care (SC) in England. As the results are based on an interim analysis, the duration of follow-up for OS is limited. Long-term data on SAEs are lacking due to the use of a cut-off at 90 days after the last dose of study medication; this is of particular importance for pembrolizumab as IRAEs may occur after treatment has terminated. The ERG highlights that the pembrolizumab treatment effect for OS, as analysed by PD-L1 subgroup, may be contingent on receipt of chemotherapy as a potential treatment effect modifier because platinum-based chemotherapy combination potentially alters PD-L1 expression.

The company's NMAs for pembrolizumab combination therapy versus SC chemotherapy comparators included trials which do not accurately reflect current clinical practice in England, as none of the trials included the use of second-line immunotherapy. In additional, some of the trials in the NMAs included some patients with a PS of 2; these patients were excluded from KEYNOTE-407.

1.4 Summary of cost-effectiveness evidence submitted by the company

The company submitted a *de novo* partitioned survival model which assesses the cost-effectiveness of pembrolizumab combination therapy versus SC chemotherapy for the first-line treatment of patients with squamous metastatic NSCLC. Whilst the CS describes a model in which the partition is defined by the presence/absence of progression, the partition in the implemented model is defined according to whether patients are receiving first-line therapy or not; in the company's model, PFS has no bearing on the incremental cost-effectiveness ratio (ICER) for pembrolizumab combination therapy versus its comparators.

The CS reports the results of two base cases analyses for the overall NSCLC population: "Base Case Analysis 1" compares pembrolizumab combination therapy against carboplatin plus paclitaxel/nab-paclitaxel (the comparator used in KEYNOTE-407), whilst "Base Case Analysis 2" presents pairwise comparisons of pembrolizumab combination therapy versus cisplatin/carboplatin in combination with docetaxel, gemcitabine or paclitaxel, based on the company's NMAs. Separate exploratory analyses are

also presented across three PD-L1 subgroups: TPS <1%, 1-49% and ≥50%. Within these subgroups, the comparator is carboplatin plus paclitaxel/nab-paclitaxel; pembrolizumab monotherapy is also included as a comparator in the PD-L1 TPS ≥50% subgroup. Across all analyses, incremental health gains, costs and cost-effectiveness are evaluated over a 30-year time horizon from the perspective of the NHS and Personal Social Services (PSS). The model parameters were informed by analyses of time-to-event data (time to treatment discontinuation [TTD] and OS) collected within KEYNOTE-407, with additional external data from the US Surveillance, Epidemiology and End Results (SEER) Program used to model long-term OS outcomes. Despite a maximum treatment duration for pembrolizumab of 2 years, the company's model assumes a lifetime treatment effect for OS for the pembrolizumab combination therapy group. The effectiveness of other SC chemotherapy comparators was estimated from the company's NMA (squamous, PD-L1 unselected population); the effectiveness of pembrolizumab monotherapy was estimated using an ITC of trimmed data from KEYNOTE-407 and KEYNOTE-042. HRQoL estimates for time-to-death categories were based on Euroqol EQ-5D data collected within KEYNOTE-407. Resource cost parameters were taken from KEYNOTE-407, standard costing sources, previous NICE technology appraisals (TAs), additional literature and assumptions. The company's economic analyses incorporate a price reduction relating to an existing Commercial Access Agreement (CAA) for pembrolizumab.

Within the overall metastatic squamous NSCLC population (PD-L1 unselected), the company's model suggests that the probabilistic ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel is £28,852 per QALY gained (company's Base Case Analysis 1); the results of the company's deterministic model are similar (ICER=£28,672 per QALY gained). Based on a fully incremental analysis of the company's model, including the correction of model errors identified by the ERG during the clarification process, the ICER for pembrolizumab combination therapy versus cisplatin/carboplatin plus gemcitabine is estimated to be £51,240 per QALY gained (company's Base Case Analysis 2). Within the PD-L1 TPS subgroups, the ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel is estimated to be in the range £25,849 to £32,174 per QALY gained.

1.5 Summary of the ERG's critique of cost-effectiveness evidence submitted

The ERG critically appraised the company's health economic analyses and double-programmed the deterministic version of the company's model (for Base Case Analyses 1 and 2 and for the PD-L1 TPS subgroup analyses). The ERG's critical appraisal identified a number of issues relating to the company's model and the evidence used to inform its parameters. The most pertinent of these include: (i) the identification of model errors; (ii) concerns relating to the company's NMAs, in particular, the absence of second-line immunotherapy from the trials of SC chemotherapy comparator regimens; (iii) uncertainty surrounding long-term extrapolation; (iv) the potentially optimistic assumption of a lifetime

OS treatment effect for pembrolizumab combination therapy; (v) the inclusion of an implicit assumption of cure within the model, and (vi) concerns regarding the company's approach to modelling HRQoL. The ERG notes that the OS data from KEYNOTE-407 are immature and alternative assumptions regarding long-term OS benefits have the propensity to increase the ICER substantially.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The systematic literature review (SLR) of clinical evidence in the CS was reported to have adhered to best practice in systematic reviewing. The KEYNOTE-407 trial is a high quality RCT and is relevant to the decision problem.

The ERG did not identify any major technical model errors which impact on the company's economic comparison of pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (company's Base Case Analysis 1).

Notwithstanding the ERG's concerns regarding the suitability of the SEER dataset, two clinical advisors to the ERG believed that the company's OS predictions for the SC chemotherapy group of the model were plausible. The third advisor suggested that OS outcomes for patients in the SC chemotherapy comparator group may be more favourable than the company's OS model predictions due to the availability of second-line immunotherapy.

1.6.2 Weaknesses and areas of uncertainty

As the KEYNOTE-407 trial does not reflect clinical practice whereby patients with strong PD-L1 expression receive first-line pembrolizumab monotherapy there is no head-to-head evidence comparing pembrolizumab combination chemotherapy with pembrolizumab monotherapy. Other than the KEYNOTE-407 trial, the trials included in the NMAs do not include second-line immunotherapy.

The presentation and analysis of safety data for pembrolizumab combination therapy are currently limited and do not provide long-term data which are relevant for IRAEs.

The company's health economic analyses are subject to several weaknesses and uncertainties:

- The progression-based partitioned survival model described in the CS does not reflect the company's implemented model. Several parameter values contained in the model were incorrectly reported in the CS, including the hazard ratios [HRs] applied in the company's Base Case Analysis 2 and the PD-L1 TPS ≥50% subgroup analysis. Some evidence sources used to inform model parameters are unclear or inconsistent between the CS and the implemented model.

- The original submitted model contained errors which render the results of the company's Base Case Analysis 2 unreliable.
- The ERG considers there to be considerable uncertainty surrounding the expected long-term survival of patients receiving pembrolizumab combination therapy or SC chemotherapy (including those who go on to receive second-line immunotherapy).
- The ERG has concerns regarding the appropriateness of using external data from SEER, together with an assumed lifetime OS treatment effect, to estimate long-term survival for pembrolizumab combination therapy. The ERG's exploratory analyses indicate that the use of alternative parametric OS models may substantially increase the ICER for pembrolizumab combination therapy compared with the company's base case estimates.

1.7 Summary of exploratory analyses and sensitivity analyses undertaken by the ERG

The ERG undertook six sets of exploratory analyses using the deterministic version of the company's model. The ERG's preferred model includes: (i) the correction of model errors; (ii) the inclusion of health state utilities defined according to the presence/absence of disease progression (together with the use of PFS data applied as the model partition); (iii) the use of disease management costs defined according to the presence/absence of disease progression; (iv) increased costs associated with second-line immunotherapy, and (v) the use of clinicians' preferred OS models. The ERG's preferred analyses combine all of these amendments and are presented across two separate scenarios: (a) an optimistic scenario, and (b) a pessimistic scenario. The ERG's optimistic scenario applies the company's piecewise KM/log logistic OS model for the pembrolizumab combination therapy group and the company's piecewise KM/SEER OS model for the SC chemotherapy group. The ERG's pessimistic scenario applies the ERG's log logistic OS model for both modelled treatment groups, based on the whole KEYNOTE-407 dataset.

The ERG's preferred optimistic scenario suggests an ICER for pembrolizumab combination therapy versus SC chemotherapy of £35,981 per QALY gained, whilst the pessimistic scenario suggests a higher ICER of £49,473 per QALY gained. Additional sensitivity analyses using the full range of ERG-fitted standard parametric models and natural cubic spline models lead to ICERs ranging from £35,981 to £274,028 per QALY gained. The ERG's exploratory subgroup analyses, which are based on the same parametric OS models as those applied in the ERG's preferred analyses for the overall population, suggest the following results:

- PD-L1 TPS <1% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £34,239 (pessimistic) to £34,392 (optimistic) per QALY gained.
- PD-L1 TPS 1-49% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £40,767 (optimistic) to £52,680 (pessimistic) per QALY gained

- PD-L1 TPS ≥50% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £39,193 (optimistic) per QALY gained to dominated (pessimistic). Pembrolizumab monotherapy is ruled out due to strong dominance.

The ERG notes that additional data collection in KEYNOTE-407 may resolve some of the uncertainty surrounding expected outcomes, both within the overall metastatic squamous NSCLC population and within specific PD-L1 TPS subgroups. Given the uncertainty in the OS estimates based on IA2 of KEYNOTE-407, it is unclear whether pembrolizumab combination therapy meets NICE's End of Life criteria.

2 BACKGROUND

This chapter presents a brief critique of the company's background to the disease and the current treatment pathway in England.

2.1 Critique of company's description of underlying health problem

The company's submission[1] (CS) presents an accurate overview of the histology and classification of non-small-cell lung cancer (NSCLC). The CS cites estimates from the American Cancer Society,[2] which suggest that NSCLC represents 85% of all lung cancer cases, with squamous NSCLC accounting for 25-30% of all lung cancer.

The indication for pembrolizumab for this Single Technology Appraisal (STA) relates to metastatic (Stage IV) disease, whereby the cancer has spread to distant lymph nodes or to other organs such as the liver, bone, or brain. Page 24 of the CS[1] states that nearly half of all lung cancer cases in England (49.7%) are diagnosed at Stage IV disease; at this point, curative surgical treatment is no longer viable and patient prognosis is poor. The clinical intent of treatment for these patients is to prolong overall survival (OS) and improve health-related quality of life (HRQoL) by improving symptoms.

The CS[1] (page 18) states that pembrolizumab binds to the programmed cell death 1 (PD-1) receptor, inhibiting ligand binding (including programmed death-ligand 1 [PD-L1]) and potentiates T-cell responses. Patients with advanced NSCLC and with a PD-L1 tumour proportion score (TPS) of 50% or greater (defined as PD-L1 expression on at least 50% of tumour cells) have been found to respond to treatment with pembrolizumab and as such are eligible for treatment with pembrolizumab monotherapy (National Institute for Health and Care Excellence [NICE] Technology Appraisal [TA] Guidance 531[3]). The CS estimates the percentage of patients with advanced NSCLC who express PD-L1 on at least 1% of cancer cells to be between 60% and 66%.

The approval of specific anti-PD-(L)1 drugs in the UK has changed the therapeutic landscape and has increased treatment options for patients with NSCLC, both in the first- and subsequent-line treatment settings.[4]

2.2 Critique of company's overview of current service provision

Treatment for patients with advanced NSCLC is guided by the tumour histological subtype, genotype, molecular biomarkers and the performance status (PS) of the patient. Chemotherapy is recommended as a treatment option for squamous NSCLC patients with a good performance status (World Health Organization [WHO] score of 0 or 1; or a Karnofsky score of 80–100), where the chemotherapy regimen

should be a combination of a single cytotoxic drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) (NICE Clinical Guideline 121).[5]

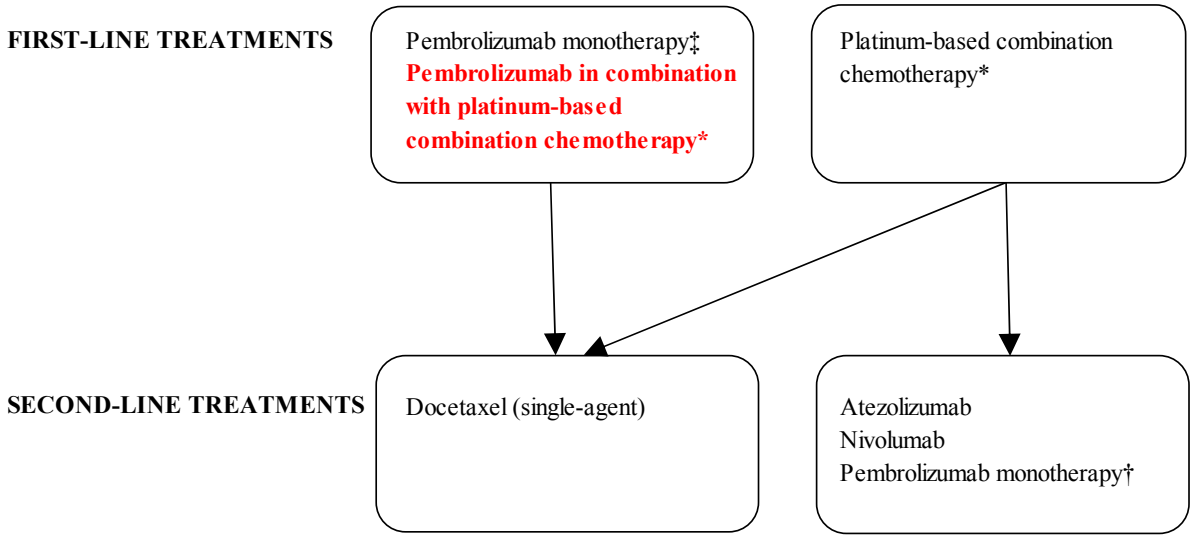
The company estimates that 7,561 patients will be diagnosed with squamous NSCLC cancer in England in 2019. Of these, the company estimates that 2,025 patients with Stage IV cancer and an Eastern Cooperative Oncology Group (ECOG) PS of 0-1 will be eligible for treatment with pembrolizumab combination therapy.

The CS (page 26) states that since PD-L1 test requisition has been incorporated into hospital treatment pathways and protocols, there has been a significant increase in the volume of PD-L1 testing in England.

Pembrolizumab monotherapy is currently recommended for PD-L1-positive (TPS ≥50%) metastatic disease in adults with untreated non-small-cell lung cancer (NSCLC) and no epidermal growth factor receptor (EGFR) activating mutations or anaplastic lymphoma kinase (ALK) gene fusions, subject to a maximum 2-year stopping rule and a confidential commercial access agreement (CAA). The company anticipates that pembrolizumab combination therapy will be positioned as an additional treatment option for patients who have advanced/metastatic, squamous NSCLC, regardless of PD-L1 expression, and a PS of 0-1 where combination platinum chemotherapy is offered.

The current treatment pathway for patients with untreated metastatic squamous NSCLC is summarised in Figure 1. The company's proposed positioning of pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel is highlighted in red. Guidelines from the National Comprehensive Cancer Network (NCCN) 2018 state that nab-paclitaxel can be substituted for paclitaxel; however, nab-paclitaxel is not available for use in this indication in England.

Figure 1: Current treatment pathway for patients with untreated metastatic squamous NSCLC and proposed positioning of pembrolizumab combination therapy



Platinum-based combination chemotherapy - gemcitabine, paclitaxel, vinorelbine plus carboplatin or cisplatin
** unless unable to tolerate platinum therapy*
† PD-L1 TPS>1% only
‡ PD-L1 TPS≥50% only
Note - treatment may involve re-challenging with platinum-based chemotherapy in second-line for some patients

Clinical advisors to the Evidence Review Group (ERG) stated that gemcitabine plus carboplatin is most commonly used as a first-line treatment in England and that carboplatin plus paclitaxel is regarded as a similar alternative regimen. They also stated that docetaxel is usually reserved for later lines of therapy.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[6] and addressed in the CS is presented Table 1.

Table 1: Company's statement of the decision problem (reproduced from CS, Table 1)

	Final scope issued by NICE	**Decision problem addressed in the CS**	**Rationale if different from the final NICE scope**
Population	Adults with untreated metastatic squamous non-small-cell lung cancer (NSCLC)	Adults with untreated metastatic squamous NSCLC	In line with the licence, based on the data from the supporting clinical trial KEYNOTE-407[7, 8]
Intervention	Pembrolizumab in combination with: • carboplatin and paclitaxel • carboplatin and nab-paclitaxel	Pembrolizumab in combination with • carboplatin and paclitaxel • carboplatin and nab-paclitaxel	In line with the licence
Comparators	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab monotherapy (for people with tumours that express PD-L1 with at least 50% tumour proportion score with no EGFR- or ALK positive tumour mutations only)	As per final scope issued by NICE	Data from KEYNOTE-407[7, 8] will provide comparative efficacy of pembrolizumab in combination with paclitaxel/nab-paclitaxel plus carboplatin. Data for comparative efficacy of pembrolizumab in combination with paclitaxel/nab-paclitaxel plus carboplatin versus remaining comparators will be derived from indirect treatment comparison (ITC).
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Duration of response • Adverse effects of treatment • Health-related quality of life.	As per final scope issued by NICE	

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial access agreements for the intervention or comparator technologies will be taken into account. If appropriate, the economic modelling should include the costs associated with diagnostic testing for biological markers (for example PD-L1) in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.	As per final scope issued by NICE	
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on the biological marker (PD-L1).	The following PD-L1 subgroups have been considered: TPS <1%, ≥1%, 1-49%, ≥50%	

NICE – National Institute for Health and Care Excellence; CS – company's submission; NSCLC – non-small-cell lung cancer; PD-L1 – programmed death-ligand 1; EGFR - epidermal growth factor receptor; ALK - anaplastic lymphoma kinase; ITC – indirect treatment comparison; TPS – tumour proportion score

3.1 Population

The overall patient population in the CS[1] relates to patients with untreated metastatic squamous NSCLC, irrespective of PD-L1 tumour expression status. This is in line with the population defined in the final NICE scope.[9] The main clinical evidence for the intervention under appraisal is drawn from a single randomised controlled trial (RCT): KEYNOTE-407.[7, 8] The population included in this study represents patients with less severe prognoses than those commonly seen in clinical practice due to the restriction to patients with ECOG PS 0 or 1. However, clinical advisors to the ERG suggested that this restriction is appropriate as patients with an ECOG PS ≥2 would not be considered suitable for treatment with immunotherapy in combination with platinum-doublet chemotherapy. The clinical advisors also highlighted that expression of the PD-L1 biomarker is a key driver in determining whether pembrolizumab treatment should be given first-line as monotherapy. One clinical advisor highlighted that they would consider using pembrolizumab combination therapy in patients with rapidly developing and bulky metastatic disease where disease progression is rapid, as this represents a group of patients for whom standard care alone may not work in time. Two clinical advisors agreed that pembrolizumab combination therapy could be a potential treatment for this subgroup with particularly aggressive disease providing that patients had TPS ≥50%.

The KEYNOTE-407[7, 8] trial was conducted in 125 centres across 17 countries, none of which were based in the UK. The majority of the study population were white (77.7%), former or current smokers (62.6%, 29.5% respectively), from countries around the world including European Union (EU) countries (45%), East Asia (19.4%) and the United States (US) (4.7%). For PD-L1 expression, approximately 35% of patients had a TPS of <1%, 37% had TPS 1-49%, and 26% had TPS ≥50%. The clinical advisors considered the study population from KEYNOTE-407[7, 8] to be broadly representative of patients seen in clinical practice in England.

As pembrolizumab combination therapy has not yet received a European/UK marketing authorisation for this indication (see Section 3.2), it is not clear which medical conditions or patient groups may be contraindicated for first-line treatment with pembrolizumab combination therapy. Patients that were excluded from the KEYNOTE-407 trial[7, 8] due to pre-existing clinical conditions may be regarded as contraindicated to pembrolizumab combination therapy; these are described in Section 4.2 of this report.

The company's base case economic analyses relate to the overall metastatic squamous NSCLC population.[1] The CS also includes economic analyses for subgroups based on PD-L1 expression (TPS <1%, TPS 1-49% and TPS ≥50%).

3.2 Intervention

Pembrolizumab (MK-3475, Keytruda®) is a monoclonal antibody manufactured by Merck Sharp & Dohme (MSD). Pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel was granted approval from the United States (US) Food and Drug Administration (FDA) on October 30th of 2018, following priority review for the proposed indication within this STA. Pembrolizumab combination therapy has not yet been granted a marketing authorisation for the first-line metastatic squamous NSCLC indication by the European Medicines Agency (EMA). Within the NSCLC population, pembrolizumab monotherapy currently holds an EU marketing authorisation for:

- First-line treatment of metastatic NSCLC for tumours that express PD-L1 with at least 50% TPS with no EGFR or ALK positive tumour mutations
- Treating locally advanced or metastatic NSCLC for tumours that express PD-L1 with at least 1% tumour proportion score after at least one prior chemotherapy regimen.

The intervention considered in the CS[1] is in line with the dosing regimen proposed within the company's marketing authorisation application: pembrolizumab administered intravenously at a fixed dose of 200mg over 30 minutes combined with carboplatin area under the curve (AUC) 6 plus paclitaxel (200mg/m^2)/nab-paclitaxel (100mg/m^2) every 3 weeks (Q3W) for 4 cycles, followed by pembrolizumab 200mg Q3W until disease progression. The KEYNOTE-407[7, 8] trial protocol mandated a maximum of 35 cycles (approximately 2 years) of pembrolizumab treatment; this is line with the FDA recommendation and is also expected to form part of the EU marketing authorisation.

The current list price for a 100mg vial of pembrolizumab is £2,630; each treatment cycle requires 2 vials (pembrolizumab acquisition cost per treatment cycle = £5,260). The company currently has a CAA in place for pembrolizumab; the acquisition cost of pembrolizumab including the CAA is [redacted] per treatment cycle (discount = [redacted]).

3.3 Comparators

The KEYNOTE-407 trial[7, 8] compares pembrolizumab combination therapy with placebo plus carboplatin and paclitaxel/nab-paclitaxel, in line with the final scope issued by NICE.[6] The dose for combination chemotherapy in both the intervention and control arms of KEYNOTE-407 was carboplatin AUC 6 mg/mL/min on day 1 of each 21-day cycle for 4 cycles and paclitaxel 200mg/m^2 on day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100mg/m^2 on days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by placebo (in the control arm) every 3 weeks.

The comparator used in Base Case Analysis 1 of the company's health economic model is based on the comparator arm of the KEYNOTE-407 trial;[7] additional platinum-based combination chemotherapy regimens are included as comparators in Base Case Analysis 2 of the company's model.

The CS[1] assumes that the carboplatin and paclitaxel/nab-paclitaxel regimen included in KEYNOTE-407 is equivalent to other platinum-based combination chemotherapy regimens in terms of clinical efficacy. The company also performed network meta-analyses (NMAs) which compare pembrolizumab combination therapy against the following chemotherapy plus platinum regimens:

- Gemcitabine plus cisplatin/carboplatin
- Paclitaxel/nab-paclitaxel plus cisplatin/carboplatin
- Docetaxel plus cisplatin/carboplatin
- Vinorelbine plus cisplatin/carboplatin.

Separate NMAs were undertaken for: (a) patients with unselected histology and unselected PD-L1 status and (b) squamous histology and unselected PD-L1. Separate analyses were presented for progression-free survival (PFS) and overall survival (OS). The latter was used in the company's health economic analysis (see Section 5.2).

The CS also compares pembrolizumab combination therapy with pembrolizumab monotherapy via an indirect treatment comparison (ITC) within the subgroup of patients with PD-L1 TPS ≥50% (the subgroup for which first-line pembrolizumab monotherapy is recommended by NICE[10]).

Clinical advisors to the ERG stated that the comparator group treatment regimens used in the studies included in the NMAs are in line with those used in clinical practice in England. They noted that nab-paclitaxel is not approved in this indication in England. In the KEYNOTE-407 trial,[7, 8] 60% of patients received paclitaxel and the remainder received nab-paclitaxel.

3.4 Outcomes

Outcomes included in the NICE scope[6] include:

- Overall survival (OS)
- Progression-free survival (PFS)
- Duration of response (DoR)
- Adverse effects of treatment (adverse events, AEs)
- Health-related quality of life (HRQoL)

The CS[1] also reports results for objective response rates (ORR, not listed in the final NICE scope). The company's model incorporates evidence from KEYNOTE-407 on OS, AEs and HRQoL. PFS outcomes

are included in the model but do not have any impact on the incremental cost-effectiveness of pembrolizumab combination therapy (see Section 5.2).

3.5 Other relevant factors

The CS[1] states that the company does not envisage any equity or equalities concerns relating to the use of pembrolizumab combination therapy in patients with untreated squamous metastatic NSCLC. As a consequence of uncertainty surrounding the currently available clinical evidence, the CS states that the company is seeking a Cancer Drugs Fund (CDF) recommendation for pembrolizumab combination therapy for the untreated metastatic squamous NSCLC population.

4 CLINICAL EFFECTIVENESS

The clinical evidence submitted by the company comprises:

- the interim results for the KEYNOTE-407 trial[7, 8]
- a systematic literature review (SLR)
- NMAs and ITCs of pembrolizumab versus relevant comparators

This chapter summarises the evidence of clinical effectiveness of pembrolizumab combination therapy from the CS[1] including the KEYNOTE-407 trial[7, 8] and the company's SLR, NMAs and ITCs.

4.1 Critique of the methods of review

4.1.1 Searches

The CS[1] reports that the SLR searches aimed to identify studies to inform direct and indirect comparisons between the interventions included in the NICE scope.[6] Searches were conducted in five phases, all of which are reported in full in CS Appendix D.[11] An appropriate range of databases was covered including NICE's recommendations of MEDLINE, EMBASE and CENTRAL. Searches were limited to citations in the English language and those published since 1995. The ERG notes that the English language limit, which was applied at the search stage rather than the sifting stage, excludes any records for which the language field was empty as well as any foreign language studies for which an English abstract was available.

Search strategies were constructed around the decision problem (CS,[1] Section B1.1, Table 1, page 17) and used a combination of subject headings and free text terms. Search filters to identify RCTs were applied; these were based on those of the Scottish Intercollegiate Guidelines Network (SIGN), albeit with some modifications (such as the exclusion of review articles). The ERG noted that a somewhat different set of search terms was used for the NSCLC disease area in the clinical effectiveness review, compared with that used in the cost-effectiveness searches. The ERG conducted brief searches comparing the yield retrieved by the two sets of NSCLC terms and found that each version retrieved results that the other had missed. As part of the clarification process (see clarification response,[12] question A1), the ERG queried the company's use of different disease terms between the clinical and cost-effectiveness searches; the company responded that they believed their approach to be "*sufficiently sensitive*."

Due to the searches being conducted over several phases, date limits were applied to the update searches. However, these are reported incorrectly in the CS;[1] this was queried by the ERG during the clarification process. The company attributed this to a "*transcription error*" (clarification response,[12] question A2). The ERG notes that no transcription would be required as search strategies are usually

reproduced directly from the interface without editing, therefore the use of such transcription raises uncertainty about the accuracy of the reporting. The CS reports that bibliographies of relevant SLRs, meta-analyses and HTA submissions were manually checked for relevant missed studies. The company's clarification response[12] (question B1) confirms that no forward tracking of included citations was conducted. Recent conference proceedings from several relevant series were consulted in order to identify unpublished literature. In addition, the company searched for unpublished but completed clinical trials using the National Institutes of Health (NIH) clinical trials register, but not the WHO International Clinical Trials Registry, as is recommended by Glanville *et al.*[13]

Despite the concerns raised above, the ERG is generally satisfied with the company's approach to the identification of evidence for the clinical effectiveness review.

4.1.2 Inclusion criteria

The inclusion criteria for the company's SLR are summarised in Table 1 (Section D1.1.1) of the CS appendices.[11]

The inclusion criteria are broadly in line with the final NICE scope.[6] The company's SLR limits included study designs to RCTs. Whilst an RCT is the appropriate study design to evaluate the clinical efficacy of pembrolizumab versus its comparators, other research designs are useful for understanding the full safety profile and acceptability of new interventions. By limiting their search to RCT evidence only, the company has excluded other study designs (for example non-randomised and non-controlled evidence) which may provide long-term and/or real-world evidence for the adverse effects of pembrolizumab. This issue is particularly relevant for pembrolizumab as the drug is an immunotherapy which causes certain immune-related side effects (such as pneumonitis) which can be severe or life-threatening and can occur even after treatment has terminated.[14] The CS[1] actively excluded systematic reviews and meta-analyses from its review of clinical effectiveness. The ERG requested clarification on the justification for this exclusion and the reliance on primary data only; in response, the company only reiterated that its aim was to focus on clinical trials (clarification response,[12] question A3). This response indicates that the company's SLR assigns little value to research which aggregates data from primary studies. The ERG considers that, in the absence of an NMA of AEs for pembrolizumab combination therapy, consideration of systematic reviews could have provided useful information on the safety profile of pembrolizumab combination therapy in relation to current standard treatments.

Table 18 of the CS[1] provides a list of studies that were excluded from the company's NMAs. The ERG notes that 27 studies were excluded with the reason for exclusion reported as "other." The company provided further clarification (clarification response,[12] question A4) on reasons why 29 citations (two

more than the 27 noted in the CS appendices[11]) were excluded. The reasons given were: review (n=19), not found (n=4), protocol (n=4), not English (n=1) and editorial (n=1).

4.1.3 Critique of data extraction

The methods of study selection and data extraction for the SLR are described in Section D.1.1.2 of the CS.[1] The CS states that this involved two reviewers who worked independently, with a third reviewer available to resolve discrepancies. The methods described are appropriate and adhere to good practice in systematic reviews according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15]

4.1.4 Quality assessment

Quality assessment is described in the CS appendices[11] (Section D.1.1.4) as having been undertaken independently by two reviewers, with a third reviewer utilised for resolution of discrepancies. The Cochrane Risk of Bias tool[16] was used to critically appraise the RCTs of interest. Overall the KEYNOTE-407 trial[7, 8] was determined in the CS to be at "low risk" of bias. The ERG considers this a generally fair judgement of this RCT (for which the Clinical Study Report [CSR] was available). A summary of the quality assessment of the KEYNOTE-407 trial, assessed using the Cochrane Risk of Bias tool, is provided in Table 11 (Section B.2.5) of the CS.[1] Methods described for randomisation were appropriate and randomisation was stratified (1:1) according to PD-L1 status, (TPS <1% vs. TPS ≥1%), choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). Concealment of allocation was appropriate as the trial used a triple-blind placebo-controlled design and therefore patients, care providers and central outcome assessors (radiologists) were unaware of treatment allocation. Patient characteristics were well balanced at baseline.

In consideration of attrition rates between study groups, the company's quality assessment states that discontinuations were similar between treatment arms. However, the ERG notes with reference to the description of safety data (CS,[1] Section B.2.10.2, page 107), that higher rates of discontinuation of any drug within the treatment regimen due to an AE occurred in the pembrolizumab combination therapy group compared with the control group (23.4% vs 11.8%). The company speculates that differences in discontinuation rates between the treatment groups may be attributable to the longer duration of exposure in the pembrolizumab combination therapy group. However, the CS also states that similar trends were observed in exposure-adjusted analyses of drug discontinuations.

The CS[1] reports intention-to-treat (ITT) analyses, which is appropriate. Whilst patients in the control arm were permitted to switch to pembrolizumab monotherapy, statistical adjustment for treatment switching was not implemented in the CS ITT base case analysis. The ERG considers this to be appropriate as second-line immunotherapy therapy is standard care in England and this treatment

switching represents what would happen in clinical practice for people who are PD-L1 positive (≥1%). Information regarding the PD-L1 status for people who switched is not provided in the CS.

The primary and secondary outcome measures in the CS[1] are in line with the final NICE scope,[6] with the exception of the Euroqol EQ-5D, whereby only the visual analogue scale (VAS) data, but not questionnaire data, are reported in the CS and the CSR for KEYNOTE-407.

4.1.5 Evidence synthesis

As only one RCT (KEYNOTE-407[7, 8], Section 4.2.2) was identified for comparing pembrolizumab combination therapy to a relevant comparator, pairwise meta-analysis was not undertaken.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Trials of interest

The CS focuses on the KEYNOTE-407 trial[7, 8] (NCT02775435) as the main source of evidence for the clinical effectiveness of pembrolizumab combination therapy in the target population (see Section 4.2.2). Other relevant trials that are mentioned in the CS[1] or its appendices[11] (without presenting results) are shown in Table 2.

Table 2: Trials related, but not directly relevant, to the decision problem addressed in the CS

Trial name NCT number	Trial description	Relevance to decision problem
KEYNOTE-042 NCT02220894	Study of Pembrolizumab (MK-3475) Versus Platinum-based Chemotherapy for Participants With PD-L1-positive Advanced or Metastatic Non-small Cell Lung Cancer	Pembrolizumab monotherapy, open-label
KEYNOTE-024[17] NCT02142738	Study of Pembrolizumab (MK-3475) Compared to Platinum-Based Chemotherapies in Participants With Metastatic Non-Small Cell Lung Cancer	Pembrolizumab monotherapy, open-label
KEYNOTE-021 NCT02039674	Study of Pembrolizumab (MK-3475) in Combination With Chemotherapy or Immunotherapy in Participants With Non-small Cell Lung Cancer	Non-squamous, pembrolizumab combination, open-label

A new and ongoing trial not mentioned in the CS[1] or its appendices[11] was by the ERG (KEYNOTE-799); whilst this study focusses on Stage III patients, it may contribute additional safety data for pembrolizumab combination therapy in the squamous NSCLC population (described in Table 3).

Table 3: Ongoing trial identified by the ERG, not included in the CS

Trial name NCT number Sponsor	Trial description	Relevance to decision problem
KEYNOTE-799 NCT03631784 MSD	Double-blind, Phase 2 RCT of Pembrolizumab in Combination with Platinum Doublet Chemotherapy and Radiotherapy in patients with unresectable, local advanced Stage III NSCLC	Began recruiting in October 2018 and not due for completion until 2020. Estimated Enrollment: 216 participants

The ERG sought advice from clinical experts on whether trials from non-squamous NSCLC (such as KEYNOTE-189, KEYNOTE-021) are relevant to the decision problem defined in the NICE scope.[6] The ERG's clinical advisors clarified that squamous and non-squamous histologies should be treated separately, largely due to the recommended chemotherapies in standard care (SC chemotherapy) being different for these populations as well being diseases with distinct clinical outcomes.

4.2.2 The KEYNOTE-407 trial

The KEYNOTE-407 trial[7, 8] (NCT02775435) is a Phase III, multi-centre, triple-blind RCT assessing the efficacy and safety of pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel versus placebo plus carboplatin and paclitaxel/nab-paclitaxel. The company presents data from this ongoing trial of 559 patients with untreated squamous NSCLC, using a second interim analysis (IA2) with data cut-off of 3rd April 2018. The CS[1] states that the final analysis for this trial is planned for [redacted]. The clinicaltrials.gov website estimates the study completion date to be February 2021. The median duration of follow-up in the KEYNOTE-407 trial at IA2 is reported to be 7.8 months (range 0.1 to 19.1 months), with 43.5% of patients remaining in the pembrolizumab combination group and 25.7% of patients in the control group remaining on assigned treatment, which includes 4 cycles (12 weeks) of platinum-based combination chemotherapy and a placebo control.

Patient eligibility for KEYNOTE-407

Key inclusion and exclusion criteria for patients entering the KEYNOTE-407 trial[7, 8] are reported in Table 5 of the CS[1] (Section B.2.3). Patients were ineligible for the trial if they had: prior systemic treatment; major surgery within 3 weeks; received radiation therapy to the lung within 6 months; completed palliative radiotherapy within 7 days; central nervous system (CNS) or brain metastases; autoimmune disease that required systemic therapy within 2 years; a medical condition that required immunosuppression; prior immunotherapy; interstitial lung disease or a history of pneumonitis. Eligible patients were: over 18 years of age; had a life expectancy of at least 3 months; had an ECOG performance status of 0 or 1; and had adequate organ function.

The ERG cross-checked the key inclusion criteria in the CS[1] with the inclusion criteria described in the CSR (page 37). The criterion "*Unable or unwilling to take folic acid or vitamin B12 supplementation*" was listed in the CS exclusion criteria but not in the CSR exclusion criteria. Clinical advice to the ERG clarified that this criterion is for pemetrexed chemotherapy used in non-squamous carcinomas, hence this is not relevant for the squamous study population.

From June 2016, 559 patients were randomised 1:1 to two treatment arms:

- *Intervention*: 278 patients received pembrolizumab 200mg and carboplatin AUC 6mg/mL/min on day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200mg/m^2 on day 1 of each cycle for 4 cycles or nab-paclitaxel 100mg/m^2 on days 1, 8 and 15 of each cycle for 4 cycles, followed by pembrolizumab 200mg every 3 weeks. Pembrolizumab was administered prior to chemotherapy on day 1.
- *Control*: 281 patients received placebo and carboplatin AUC 6mg/mL/min on day 1 of each 21-day cycle for 4 cycles and paclitaxel 200mg/m^2 on day 1 of each cycle for 4 cycles or nab-paclitaxel 100mg/m^2 on days 1, 8 and 15 of each cycle for 4 cycles, followed by placebo every 3 weeks.

All treatments were administered intravenously. Treatment continued until disease progression, as assessed by blinded independent central review using response evaluation criteria in solid tumours (RECIST) v1.1[18] criteria (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ), unacceptable toxicity, or a maximum of 35 cycles of pembrolizumab (24 months). Patients randomised to the control arm were offered pembrolizumab monotherapy at the time of disease progression. However, there was no pembrolizumab monotherapy comparator arm in the KEYNOTE-407 trial for those with strong PD-L1 expression (TPS ≥ 50%), as is used in current clinical practice in England.

The baseline characteristics of the study population are described in Table 7 (Section B.2.3) of the CS.[1] The median age was 65 years (range: 29 to 88 years), 81% were male and 93% were former or current smokers. The majority of patients were white (77%) and most had an ECOG PS of 1 (71%). Thirty-five percent of patients had tumour PD-L1 expression TPS <1%; 19% were from the East Asian region, 60% of patients received paclitaxel whilst the remainder received nab-paclitaxel.

Interim analysis 2

Study results presented in the CS[1] are based on IA2 of the trial (data cut-off 3rd April 2018). Clinical advisors to the ERG questioned the appropriateness of appraising the trial data before the study has completed considering the low numbers of patients in the analyses after 12 months. The ERG requested clarification from the company on the power of IA2 to detect significantly significant differences in OS

and PFS because the CS describes the power of the study to detect significant hazard ratios (HRs) for the final analysis, but not at IA2. The company responded that for PFS, with [redacted] events at IA2, the study has *"... ~ [redacted] power for detecting a HR of [redacted] at [redacted] (one-sided) significance level"* (clarification response,[12] question A9). The actual number of events observed are 349 for PFS. For OS, with [redacted] deaths, the study has ~[redacted] power for detecting a HR of [redacted] at [redacted] (one-sided) significance level. The actual number of events observed is 205 for OS (CS, page 41). The ERG notes that the number of events required for the pre-specified efficacy boundary in OS at IA2 has not been met.

The key efficacy endpoints are described in Table 9 (Section B.2.4) of the CS[1] as PFS and OS. Secondary endpoints are ORR and DoR. An exploratory efficacy endpoint using patient reported outcome measures (PROMs) is also described on page 36 of the CS, based on the EQ-5D VAS. The company clarified that the EQ-5D-3L questionnaire was used to inform HRQoL parameters in the model (see Section 5.2.2); results of this analysis are not presented in the clinical section of the CS. The European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (EORTC QLQ-C30) and the EORTC quality of life questionnaire for lung cancer (EORTC QLQ-LC13) were also reported to have been used in the trial, but results are not provided in the CS.

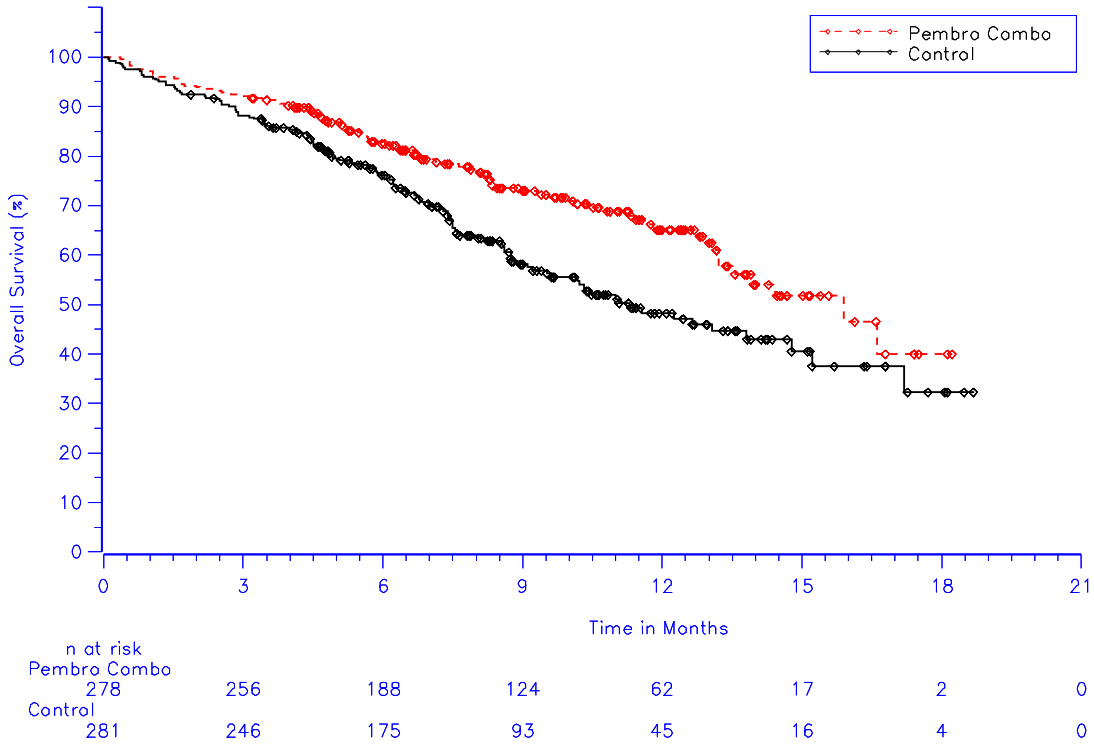
At IA2, the mean number of cycles of treatment received was [redacted] (standard deviation [SD] [redacted]) and [redacted] (SD [redacted]) in the pembrolizumab combination and placebo control groups, respectively. At this point of the trial, 75 patients in the control group had switched to pembrolizumab monotherapy. An additional 14 patients are described (CS,[1] page 52) as receiving a PD-1 antibody (pembrolizumab or nivolumab) as subsequent therapy outside of the study, resulting in a switching rate of 42.6% (89/209), whilst 72 patients were reported as remaining in the control group. Adjustment for treatment switching was not implemented in the CS ITT base case analysis for the patients who went on to receive pembrolizumab monotherapy; this is appropriate because second-line immunotherapy therapy is standard care in England for the target population (if PD-L1 TPS ≥1%).

Overall survival

OS is defined in the CS[1] (Section B.2.6.2) as time from randomisation to death due to any cause. At the time of the data cut-off for IA2, 205 deaths (38%) had been reported in the study: 85 (30.6%) deaths were reported in the pembrolizumab combination therapy group and 120 (42.7%) deaths were reported in the control group. The HR for OS was 0.64 (95% confidence interval (CI): 0.49, 0.85; p=0.0008) in favour of pembrolizumab combination therapy. Within the ITT population, median OS was 4.6 months longer in the pembrolizumab combination group compared with the control group (15.9 months versus 11.3 months; see Kaplan-Meier [KM] curves presented in Figure 2). The CS also presents OS by PD-L1 expression as a subgroup analysis, which demonstrates that median OS was longer in the

intervention group than the control group for each PD-L1 subgroup: TPS <1% (15.9 vs 10.2 months); TPS 1 to 49% (14.0 vs 11.6 months) subgroups (see Figure 3). In the PD-L1 TPS ≥50% subgroup, median OS was not reached in either the pembrolizumab combination group or the control group. The KM curves for the PD-L1 subgroups are in shown in Figure 3.

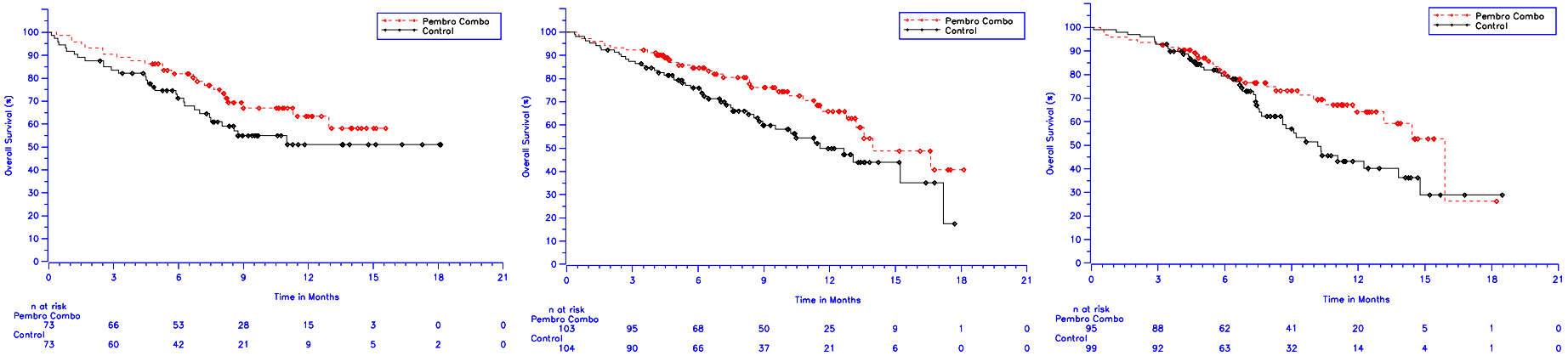
Figure 2: KM estimates of OS, ITT population (reproduced from CS Figure 4)



PD-L1 expression

Clinical advisors emphasised that, ideally the KEYNOTE-407 trial[7, 8] would have included an additional study arm for pembrolizumab monotherapy for patients with strong PD-L1 expression (TPS ≥50%) to compare combination chemotherapy therapy results with those for patients who are known to respond to pembrolizumab monotherapy. From the KEYNOTE-407 trial, the benefit of pembrolizumab combination therapy (as opposed to pembrolizumab monotherapy) in the PD-L1 strong expression subgroup is currently unclear. A further key issue highlighted by the clinical advisors to the ERG was that under current funding restrictions, patients in England may receive treatment with only one immunotherapy drug. If pembrolizumab combination therapy is recommended by NICE (irrespective of PD-L1 status), there may be uncertainty about whether it is optimal to offer first-line pembrolizumab combination therapy to patients who do not have strong PD-L1 expression (TPS <1-49%), or to reserve immunotherapy as a treatment option at second-line, given the additional toxicity burden of pembrolizumab in addition to SC chemotherapy.

Figure 3: KM for OS ITT population by PD-L1 TPS subgroup (reproduced from CS Figures 6, 7 and 8)



TPS ≥50% **TPS 1-49%** **TPS<1%**

The KM plots indicate that the intervention and control curves separated earlier in those with an increased PD-L1 expression (at month 0 for TPS ≥50%, after 2 months for 1-49%, and after 7 months for TPS <1%). This trend indicates that those with higher PD-L1 TPS have an immediate treatment response to pembrolizumab combination therapy. By contrast, the KM curve for the TPS PD-L1 <1% subgroup shows that the pembrolizumab combination arm languishes under and around the control arm until month 7; this indicates a delayed treatment response. Clinical advice received by the ERG suggests that platinum-doublet chemotherapy treatment, as provided in the control arm of the trial, can drive up tumour expression of PD-L1, or increase immunogenicity, as cancer cells may use the PD-1 pathway to hide from immune cells. Therefore, the apparent treatment response which occurs at around 6-7 months in the TPS <1% subgroup may be a function of PD-L1 expression increasing in response to chemotherapy. The PD-L1 TPS 1-49% subgroup demonstrates congruence to this theory, with a moderately differentiated treatment response in the intervention arm becoming apparent at around 3 months. Late emergence of a treatment response to pembrolizumab in the TPS <1% subgroup might suggest that second-line treatment with pembrolizumab would provide a similar treatment effect to those with strong PD-L1 expression. Clinical advice to the ERG was that a subgroup analysis of patients in KEYNOTE-407 with low PD-L1 expression (TPS<1%) that switched to receive immunotherapy would be informative (particularly as, in England, these patients would be eligible for atezolizumab). These data are however not provided in the CS.[1]

The ERG undertook a brief inspection of academic literature in Google Scholar for evidence to validate the notion that PD-L1 expression may alter following chemotherapy, as this represents a treatment effect modifier. A few relevant studies with small numbers of patients reported that chemotherapy altered PD-L1 expression during or after chemotherapy; however, the direction of alteration varied depending on the drugs used and the timepoint of assessment. For example, McDaniel *et al* (2016)[19] found that levels of PD-L1 increased following neoadjuvant chemotherapy (cisplatin in 13 patients, carboplatin in 26 patients). Leduc *et al* (2018)[20] found that docetaxel, platinum and fluorouracil induction chemotherapy increased PD-L1 expression. Katsuya *et al* (2016)[21] reported increases in both PD-L1 and PD-1 scores after chemotherapy with a range of drug regimens including cisplatin, carboplatin, paclitaxel, and gemcitabine. However, some studies noted a decrease in PD-L1. Rojko *et al* (2018)[22] found a significant decrease in PD-L1 expression in patients who received cisplatin-gemcitabine combination therapy (p=0.020), but no decrease was observed in the carboplatin-paclitaxel group (the chemotherapy regimen used in the KEYNOTE-407 trial[7, 8]). Lim *et al* (2018)[23] noted that PD-L1 decreased significantly after neoadjuvant chemotherapy with fluorouracil/cisplatin. Whilst this cursory analysis of empirical evidence on this topic is limited, there are emerging suggestions in the published literature that PD-L1 status alters during or following chemotherapy, depending on the chemotherapy drugs used. This may be relevant to UK practice where drug regimens other than that included in the KEYNOTE-407 trial[7, 8] are used because other chemotherapy regimens may not produce

this potential alteration to PD-L1 expression, which may affect treatment response to pembrolizumab. Clinical advisors to the ERG consequently emphasised the importance of adhering to the treatment regimens used in the KEYNOTE-407 trial if a positive recommendation for pembrolizumab is issued.

The ERG sought clinical advice on which chemotherapy comparators are most commonly used in clinical practice. The clinical advisors acknowledged that the platinum-based combination chemotherapy regimens are regarded as broadly similar and that carboplatin/gemcitabine is frequently used in England, followed by carboplatin/vinorelbine or carboplatin/paclitaxel. Whilst efficacy is regarded as generally similar between comparators, cisplatin was noted as only being suitable for a subset of fitter patients due to its particular toxicity profile. As highlighted above, it is unclear from the evidence presented in the CS[1] whether treatment response to pembrolizumab with or following standard care (SC) chemotherapy treatment with other comparators such as gemcitabine plus carboplatin would mirror the findings of KEYNOTE-407[7, 8] for the three PD-L1 subgroups.

Progression-free survival

PFS is defined in Section B.2.6.3 of the CS,[1] as time from randomisation to the first documented disease progression (as per RECIST 1.1) or death due to any cause, whichever occurs first, expressed in days. Patients without an event (progression or death) at the time of last tumour assessment were considered right censored at the last disease assessment date. At the cut-off date for IA2, 349 (62%) PFS events had been reported. Data are provided for PFS within each treatment arm with 152 (54.7%) events reported in the pembrolizumab combination therapy group and 197 (70.1%) events reported in the control group. Median PFS for pembrolizumab combination therapy was 6.4 months (95% CI 6.2 to 8.3 months) compared with 4.8 months (95% CI 4.3 to 5.7) for control (difference of 1.6 months). KM estimates for PFS based on blinded independent central review of RECIST 1.1 criteria are provided on pages 58 and 64 of the CS. The CS reports that this is a statistically significant difference and equates to a 44% reduction in risk of progression or death for the pembrolizumab combination compared with the control (HR 0.56; 95% CI: 0.45 to 0.70; p<0.0001).

Objective response rate

ORR is defined as the proportion of subjects who have a complete response (CR) or a partial response (PR) based on blinded independent review using RECIST 1.1 criteria (CS,[1] Section B.2.6.4). Pembrolizumab combination therapy was reported to improve ORR compared with the control group (57.9% vs 38.4%); this difference was statistically significant (19.5% difference; p<0.0001).

Duration of response and time to response

DoR is defined as the time from the first documented evidence of complete response (CR) or partial response (PR) until disease progression or death (CS,[1] Section B.2.6.5). Time to response (TTR) is

defined as the time from randomisation to the first assessment of a CR or PR. Only confirmed CR/PRs (using RECIST 1.1) are reported to be included in the analysis for TTR and DoR. Subjects without progressive disease or death were censored at the time of last tumour assessment. Pembrolizumab combination therapy was reported to yield a longer median DoR compared with the control group (7.7 months versus 4.8 months). There was no difference in TTR between treatment groups (median 1.4 months in each group; *p*-value not reported).

Patient reported outcomes

According to the CS[1] (Section B.2.6.6), HRQoL was measured using three PROMs: (i) the EORTC QLQ-C30; (ii) the EORTC QLQ-LC13, and (iii) the EQ-5D-3L VAS. PROMs were reported to have been employed on the full analysis set (FAS) population (n=554), which consisted of all randomised patients who received at least one dose of study medication and completed at least one PROM assessment. The CS does not provide results for the EORTC QLQ-C30 or the EORTC QLQ-LC13. With respect to the EQ-5D VAS, data for two timepoints are provided: week 9 and week 18. No significant difference between treatment groups was noted using the EQ-5D VAS at week 9. At week 18, a statistically significant difference in EQ-5D scores was noted (least squares mean [LSM] [redacted]; 95% CI [redacted], *p*=[redacted]) with the pembrolizumab combination group showing a slight increase over baseline (LSM [redacted]; 95% CI [redacted]), and the control group showing a slight decrease (LSM [redacted]; 95% CI [redacted]). Results for the EQ-5D questionnaire were not reported in the CS.

4.2.3 Safety of pembrolizumab combination therapy

Safety analyses

Safety analyses presented in the CS[1] comprise data from the all-patients-as-treated (ASaT) population in KEYNOTE-407.[7, 8] This dataset consisted of all randomised patients who received at least one dose of study treatment (n=558). Incidence of, causality and outcome of AEs, Grade 3-5 AEs, serious adverse events (SAEs) and adverse events of special interest (AEOSI) were also collected in the study.

AEs were collected up to 30 days and SAEs up to 90 days after the last dose of study medication. The ERG requested a summary of AEs and SAEs that occurred after 90 days from the company during the clarification process because the Keytruda website[14] highlights that the drug *"can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. These problems may happen any time during treatment or even after your treatment has ended."* The company responded that they "*can only access the locked KN407 database with cut-off* [redacted] *and retrieve information recorded up to this cut-off. In the locked database, there is* [redacted] *in the combination arm who has* [redacted] *non-serious AEs that occurred +90 days treatment discontinuation. In the control arm there are several incidences*" (clarification response,[12] question A7). This information is

too vague and incomplete to be given full consideration. The ERG considers that AE data should be collected and reported for the full trial duration due to the known delay in AEs occurring in immunotherapy. For example, Wang *et al* (2018)[24] found 17 cases whereby cutaneous AEs developed at a median of 4.2 months after drug initiation with anti-PD-1 treatment with pembrolizumab, nivolumab, or ipilimumab.

For patients who switched from control to pembrolizumab monotherapy or another immunotherapy drug (89/209, 42.6%) AEs were censored at time of switching. The ERG considers that presenting the additional safety data from the 75 patients who switched to pembrolizumab in the KEYNOTE-407 trial[7, 8] as a separate group would have provided a more comprehensive toxicity profile for pembrolizumab considering the short duration of the available trial data.

Adverse events in KEYNOTE-407

A summary of AEs is provided in Table 46 (Section B.2.10.2) of the CS[1] and the safety profiles are noted by the company to be generally consistent with the known safety profiles of the respective therapies administered.

The incidence of SAEs was similar but numerically higher with pembrolizumab combination therapy ([redacted]) compared with control ([redacted]). Serious drug-related AEs were also higher with pembrolizumab combination therapy ([redacted]) than with control ([redacted]). The most frequently reported SAEs (incidence ≥1% in either treatment group) were generally comparable between the two groups, except colitis, which was higher in the pembrolizumab combination therapy group (pembrolizumab combination: [redacted]; control: [redacted]), and hypercalcemia, which was higher in the control group (pembrolizumab combination: [redacted] control: [redacted]).

AEs that led to death occurred in 23 (8.3%) patients in the pembrolizumab combination therapy group and in 18 (6.4%) patients in the control group. The proportion of deaths considered by a trial investigator to be attributed to a drug-related AE was 3.6% in the pembrolizumab combination therapy group compared with 2.1% in the control group.

Adverse events of special interest

The incidence of AEOSIs was higher in the pembrolizumab combination therapy group (28.8%) than the control group (8.6%). The most frequent AEOSIs (>5%) were hypothyroidism (7.9% vs 1.8%), hyperthyroidism (7.2% vs 0.7%), and pneumonitis (6.5% vs 2.1%) for pembrolizumab combination versus control respectively (CS,[1] Table 53). These events are regarded as immune-related adverse-events (IRAEs). The incidence of Grade 3 to 5 AEs was similar in the pembrolizumab combination group (69.8%) and the control group (68.2%), except for pneumonitis (pembrolizumab combination:

2.5%; control: 0.4%) and autoimmune hepatitis (pembrolizumab combination: 1.8%; control: 0.0%), which occurred more frequently in the pembrolizumab combination therapy group than the control group. Pneumonitis is an umbrella term encompassing several AEOSIs in the CSR, including acute interstitial pneumonitis, interstitial lung disease, pneumonitis, idiopathic pneumonia syndrome, and organising pneumonia.

Whilst anti-PD-(L)1 drugs may be considered as being less toxic than platinum-based combination chemotherapy,[25] they result in different AEs to chemotherapy drugs.[26] The ERG notes that IRAEs often typically have a delayed onset and prolonged duration compared to AEs from chemotherapy[27] and that some disease-specific HRQoL questionnaires such as EORTC QLQ may not encompass the impact of these side-effects (such as cutaneous AEs).[28, 29] The presence of two relatively discrete toxicity profiles of pembrolizumab monotherapy and chemotherapy indicates that pembrolizumab combination therapy will lead to an AE profile with a cumulative burden for the two treatment regimens, consistent with the different mechanisms of action for each drug. NSCLC patients are typically older, with frequent comorbidities and treatment is usually palliative with the main goal of improving HRQoL; therefore, limiting toxicity in this patient group is of paramount importance.[26] The ERG's search for additional evidence regarding the safety of pembrolizumab highlighted a number of relevant real-world studies and secondary data analyses of AEs in pembrolizumab emphasising the incidence of IRAEs such as pneumonitis, colitis, hepatitis, thyroid disorders and Type 1 diabetes mellitus with pembrolizumab.[30-33] Additionally some endocrine toxicities, such as hypothyroidism, which are known to occur more frequently with pembrolizumab, can be permanent and require lifelong treatment.[34]

Discontinuation

Higher rates of discontinuation of any drug within the treatment regimen due to an AE occurred in the pembrolizumab combination group compared with the control group (23.4% vs 11.8%). This is noted in the CS[1] as being primarily driven by a higher rate of discontinuation of pembrolizumab (17.3%) compared with placebo (7.9%). The company speculates that *"the differences in discontinuation rates between the treatment groups may be attributable to the longer duration of exposure in the pembrolizumab combination"* (CS,[1] Section B.2.10.2, page 107). However, the CS also states that similar trends were observed in exposure-adjusted analyses of drug discontinuations. Discontinuation of all drugs due to an AE was [redacted] in the pembrolizumab combination therapy group and [redacted] in the control group. Similar trends were reportedly observed for discontinuations due to drug-related AEs, SAEs, and serious drug-related AEs.

IRAEs occasionally require cessation of immunotherapy therapy and initiation of treatment with immunomodulatory medications (such as steroids). Published literature on this topic highlights uncertainty over how long-term steroid therapy to treat IRAEs may affect the disease course or

treatment efficacy.[35] Some retrospective studies posit that IRAEs may actually correlate with treatment response.[36] In addition, the effect of stopping and/or re-initiating pembrolizumab is not considered in the CS;[1] however, a paper by Ksienski *et al* (2018)[37] indicates that treatment interruption due to or IRAEs is correlated with lower OS in PD-L1 therapy (pembrolizumab or nivolumab). These real-world studies highlight issues regarding IRAEs, their potential to lead to treatment discontinuation and subsequent impacts on treatment response, or loss of HRQoL in the final months of life, which are not explored in the CS.

Summary of safety data

The ERG considers that the data presented for the safety of pembrolizumab combination therapy in the CS,[1] namely from the KEYNOTE-407,[7, 8] were limited because KEYNOTE-407 is an incomplete trial. Separate AE data for patients who switched to pembrolizumab monotherapy are not presented in the CS, further limiting the long-term safety data available from the key relevant trial. This is particularly relevant since pembrolizumab is an immunotherapy which causes immune-related side effects that can be severe or life-threatening and can occur even after treatment has terminated.[14] During the clarification stage of the appraisal, the ERG requested that the company either provide summary data or perform an NMA of treatment-related Grade 3/4 AEs including KEYNOTE-407, KEYNOTE-024 and KEYNOTE-042 trials (see clarification response,[12] question A6). The company's response provided summary data for the trials requested which were assessed by the ERG. The numeric AE data were comparable between pembrolizumab monotherapy and chemotherapy in the KEYNOTE-024 and -042 trials, but with consistently higher discontinuations in the pembrolizumab treatment arm. Whilst these data from two trials of pembrolizumab monotherapy are not directly applicable to the decision problem, the ERG notes that pembrolizumab and chemotherapy combination therapy have different mechanisms of action. Therefore, patients undergoing pembrolizumab combination therapy, as well as benefiting from the two different treatment effects, are likely to accumulate the burden of both of these different AE profiles. As well as discontinuation of therapy, many patients will require cessation of treatment and systemic steroids at some point during their treatment to manage immune-IRAEs; the long-term implications of such treatment interruptions are currently uncertain.

The SLR presented in the CS[1] was restricted to RCTs without consideration of non-randomised evidence or systematic reviews and no NMA of AEs was performed. Therefore, the ERG regards the safety analyses contained in the CS to reflect a 'light-touch' approach, considering the lack of long-term safety data from clinical trials of anti-PD-1 therapy.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS[1] relies on evidence from the key ongoing trial (KEYNOTE-407[7, 8]) as the primary source of evidence for the efficacy and safety of pembrolizumab combination therapy. As direct head-to-head evidence of pembrolizumab combination therapy is only available versus placebo plus carboplatin and either paclitaxel/nab-paclitaxel from this trial, the company presented two indirect treatment comparison (ITC) analyses of relevant comparators:

- ITC1 - pembrolizumab combination therapy versus chemotherapy comparators
- ITC2 - pembrolizumab combination therapy versus pembrolizumab monotherapy.

As part of ITC1, two separate NMAs were conducted to provide comparative efficacy data:

- NMA1 - including trials with purely squamous, PD-L1 unselected patients.
- NMA2 - including trials with both squamous and non-squamous patients, unselected for PD-L1. In the CS,[1] this is referred to as trials including patients who are "*unselected for histology*" (CS, page 82). Meta-regression was employed to estimate the treatment effect for patients from these trials with squamous disease only.

Details of the identification and methodology of the trials included in the company's ITC analyses are described below.

4.3.1 Search strategy

The trials included in the company's ITCs were identified from the SLR searches described in Section 4.1.1.

4.3.2 Study selection criteria

The CS[1] states that the relevant RCTs identified in the SLR were included in a feasibility assessment for the NMAs. The CS does not explicitly state whether the inclusion criteria for the ITC were identical for the SLR. The ERG does not consider that any eligible trials have been missed.

Feasibility assessment

Thirty-six RCTs were identified as relevant for the NMAs from the company's SLR; these studies were then subjected to a feasibility assessment (CS Appendix D,[11] page 118). It should be noted that this assessment was performed only for ITC1 and no separate assessment was reported for ITC2. Five of the 36 eligible RCTs were conducted in purely squamous patients (CTONG1002,[38, 39] KEYNOTE-407,[7, 8] Kristensen *et al*., 2017,[40] NAVotrial03,[41] and Saad *et al*., 2017[42]), with the remaining 31 trials conducted in patients unselected for histology. Following the feasibility assessment, 11 trials were

excluded from ITC1 on the basis of lack of comparability. Comparability was assessed in terms of disease histology and other prognostic factors. Three trials (Ahmed *et al*., 2017,[43] ECOG 1599, and Khodadad *et al*., 2014[44]) were excluded from the unselected for histology analysis (ITC1, NMA2) because most enrolled patients had an ECOG PS of 2. Whilst this is an appropriate reason to exclude trials, some trials which did include some patients with an ECOG PS of 2 were included, and a cut-off point for the number of ECOG PS 2 patients permitted within trials is not presented or justified in the CS appendices. Three trials (Chen *et al*., 2006,[45] Kristensen *et al*., 2017,[40] and NVALT-3[46]) were excluded as they were conducted exclusively in elderly patients, but no age cut-off was discussed. A further three trials (NAVotrial03,[41] GOIM 2608,[47] and Sumanth *et al*., 2008[48]) were excluded as they did not provide HRs or KM plots for OS or PFS. Both KEYNOTE-024[17] and KEYNOTE-042[49] were excluded from the ITC1 analysis, as pembrolizumab monotherapy is only indicated in patients with high PD-L1 expression (PD-L1 ≥ 50%) in England and the target population for the analyses conducted included patients not selected by PD-L1 expression. KEYNOTE-024[17] was excluded from ITC2 as only a small number of relevant patients (n=5) received paclitaxel plus carboplatin. KEYNOTE-042[49] and KEYNOTE-407[7, 8] were included in ITC2. These trials were selected in order to compare pembrolizumab combination therapy with pembrolizumab monotherapy; this is in line with the final NICE scope.[6] A total of twenty-five studies were included across all ITC analyses. Although the ERG considers the reasons for the exclusion of trials in the feasibility assessment to be broadly appropriate, insufficient detail was provided to enable a full assessment of some of these decisions regarding study inclusion.

4.3.3 Studies identified

The CS[1] does not explicitly list the RCTs included in each NMA. Additionally, the methods and some of the results tables are presented prior to the exclusion of the eleven RCTs following the feasibility assessment for ITC1.

ITC1, NMA1: Squamous, PD-L1 unselected (fixed effect NMA)

The CS[1] states (pages 84 and 86) that three trials were included in NMA1 (ITC1) and that these trials were conducted exclusively in patients with squamous histology, which is in line with the final NICE scope.[6] However, the network diagram (CS, Figure 21, page 84) indicates that three trials (Saad *et al*., 2017;[42] ECOG 1594;[50-52] and KEYNOTE 407) were used for OS, whilst four trials are used for PFS, with the addition of the CTONG1002 trial.[38, 39] Furthermore, ECOG 1594,[50-52] included both squamous and non-squamous patients. . One trial (KEYNOTE-407[7, 8]) contained data on pembrolizumab combination therapy and three contained data on the comparators (ECOG 1594;[50-52] Saad *et al*., 2017;[42] CTONG 1002[38, 39]). Carboplatin was the only common regimen component across all studies.

Table 4: Study and patient characteristics for ITC1 NMA1 (adapted from CS Appendix D, Tables 24 and 25)

Trial ID	Treatment	N randomised	Age (years)	Male (%)	ECOG 0/1 (%)	ECOG 2 (%)	Stage IIIB (%)	Stage IV (%)
KEYNOTE-407[7, 8]	pembro + carb + nab/pac	278	65 (29-87)	220 (79)	--	--	--	--
	carb + nab/pac	281	65 (36-88)	235 (84)	--	--	--	--
Saad *et al*., 2017[42]	cis + gem	36	NR	26 (72)	194 (95)	--	--	167 (81)
	carb + gem	35	NR	29 (83)	184 (92)	--	--	164 (82)
CTONG 1002[38, 39]	carb + pac	57	NR	--	--	--	--	--
	carb + gem	62	NR	--	--	--	--	--
ECOG 1594[50-52]	cis + doc	304	63 (34-84)	192 (63)	286 (94)	18 (6)	43 (14)	261 (86)
	cis + gem	301	64 (32-87)	187 (62)	286 (95)	15 (5)	42 (14)	259 (86)
	cis+ pac	303	62 (27-84)	194 (64)	285 (94)	18 (6)	33 (11)	270 (89)
	carb + pac	299	63 (30-85)	185 (62)	284 (95)	15 (5)	42 (14)	257 (86)

pembro - pembrolizumab; carb - carboplatin; cis - cisplatin; ECOG - Eastern Cooperative Oncology Group; NR – not reported

KEYNOTE-407[7, 8] is described in Section 4.3 of this report. Saad *et al*. (2017)[42] is a prospective, randomised, controlled, open-label trial which is described as ongoing and data are presented for the period from January 2012 to December 2015. The trial was conducted in Egypt; details relating to the number of centres is not provided in the CS[1] or in Saad *et al* (2017).[42] ECOG 1594[50-52] is reported as a randomised, multicentre trial that was conducted in the US. Although details of trial initiation and completion are not reported in the CS, Schiller *et al*. (2002)[51] reports that patients were enrolled into the study between October 1996 and May 1999. CTONG 1002[38, 39] is reported in the CS as a Phase II, open-label, multicentre trial conducted in China. An abstract of the trial reported that patients were randomised to the trial between November 2010 and June 2013.[39] The study designs appear consistent with the NICE scope;[6] however, none of the studies were conducted in the UK. Whilst three of the studies were conducted recently, ECOG 1594[50-52] was conducted between 1996 and 1999. The studies broadly represent best practice in England, but exclude the current use of first-or second-line immunotherapy in those with PD-L1 expression.

Eligibility criteria of the included studies are outlined in the CS Appendix D[11] (pages 96-97). Across all four studies, patients had to be aged 18 years or over. CTONG1002[38, 39] was the only trial to have an upper age cut-off (85 years). CTONG1002[38, 39] and ECOG 1594[50-52] included patients with Stage IIIB and IV disease, whilst for KEYNOTE-407[7, 8] and Saad *et al*. (2017),[42] only those with Stage IV disease

were eligible. KEYNOTE-407[7, 8] and CTONG1002[38, 39] limited patient eligibility to those with an ECOG PS of 0-1. Comparability of baseline population characteristics for all trials included in the ITCs is summarised on pages 92-93 of CS Appendix D. The ERG notes the following issues in terms of baseline comparability. Those with ECOG PS 0-2 were eligible for inclusion in the Saad *et al*. (2017) trial[42] and, initially in, ECOG 1594.[50-52] Eligibility criteria were amended in ECOG 1594[50-52] to include only those with an ECOG PS of 0 or 1 due to the high rate of SAEs in patients with a PS of 2, with 66 patients with an ECOG status of 2 included in the analysis. Further, although not detailed in the CS,[1] according to the Saad *et al*. (2017) publication,[42] eight patients (22.2%) in the gemcitabine/cisplatin group and 11 (31.4%) patients in the gemcitabine/carboplatin group had an ECOG PS of 2 at baseline. By including patients with an ECOG PS of 2, studies may have introduced bias in terms of disease severity or a different AE profile in different arms, although it appears that patients with ECOG PS of 2 were evenly distributed across the arms of the trials. Saad *et al*. (2017)[42] and CTONG1002[38, 39] present limited details of patient characteristics at baseline, therefore it is difficult to assess if there is baseline comparability. Saad *et al*. (2017)[42] does not report mean age at baseline, but provides numbers of patients who were younger or older than 55 years of age. CTONG1002[38, 39] does not report details regarding the age of the patients at baseline. It is also difficult to assess comparability and generalisability to the English population in terms of ethnicity due to limited reporting. No trials included in NMA1 were conducted in the UK.

ITC1, NMA2: Unselected for histology, PD-L1 unselected (fixed and random effects)

In addition to three of the studies included in NMA1 (Saad *et al*., 2017;[42] ECOG 1594;[50-52] KEYNOTE-407[7, 8]), the CS[1] (page 87) reports that 20 further trials were included in NMA2. Twenty-three trials evaluating nine treatments were included in the NMA for OS and of these, 18 trials evaluating eight treatments were included in the NMA for PFS. However, the CS does not provide a definitive list of the trials included in NMA2. By scrutinising the network diagrams (CS Figures 23, page 88; Figure 24, page 92), the ERG has assumed that the trials detailed in Table 5 were included.

Table 5: Study and patient characteristics of RCTs included in ITC1 NMA2 (adapted from Tables 24 and 25 – CS Appendix D1.2.2)

Trial ID	Treatment	N randomised	Age	Male (%)	ECOG 0/1	ECOG 2	Stage IIIB (%)	Stage IV (%)
Chang *et al*, 2008[53]	cis + gem	34	62.4 (34-81)	24 (71)	18 (53)	16 (47)	9 (26)	25 (74)
	cis + vin	39	61.6 (23-85)	10 (26)	25 (64)	14 (36)	14 (36)	25 (64)
Chen *et al*, 2004[54]	cis + pac	70	64.9 (37-NA)	56 (80)	39 (56)	19 (27)	19 (27)	46 (66)
	cis + vin	70	64.8 (23-NA)	46 (66)	37 (53)	16 (23)	16 (23)	48 (69)
Chen *et al*, 2007[55]	cis + vin	48	64.9 (35-83)	35 (73)	40 (83)	8 (17)	8 (17)	40 (83)
	cis + doc	46	60.2 (32-81)	26 (57)	33 (72)	13 (28)	9 (20)	37 (80)
Comella *et al*, 2000[56]	cis + gem + vin	60	62 (38-70)	58 (97)	60 (100)	0 (0)	26 (43)	34 (57)
	cis + vin	60	61 (35-70)	56 (93)	60 (100)	0 (0)	26 (43)	34 (57)
	cis + gem	60	60 (38-70)	54 (90)	60 (100)	0 (0)	24 (40)	36 (60)
	carb + gem	62	NA	--	--	--	--	--
Douillard *et al*, 2005[57]	cis + doc	115	58 (27-75)	96 (83)	97 (84)	18 (16)	0 (0)	115 (100)
	cis + vin	118	57 (27-77)	95 (81)	101 (86)	17 (14)	0 (0)	118 (100)
ECOG 1594[50-52]	cis + doc	304	63 (34-84)	192 (63)	286 (94)	18 (6)	43 (14)	261 (86)
	cis + gem	301	64 (32-87)	187 (62)	286 (95)	15 (5)	42 (14)	259 (86)
	cis+ pac	303	62 (27-84)	194 (64)	285 (94)	18 (6)	33 (11)	270 (89)
	carb + pac	299	63 (30-85)	185 (62)	284 (95)	15 (5)	42 (14)	257 (86)
EORTC 08975[58]	cis + pac	159	57 (27-75)	95 (60)	140 (88)	19 (12)	29 (18)	130 (82)
	cis + gem	160	57 (28-75)	113 (71)	142 (89)	18 (11)	33 (21)	126 (79)
	gem + pac	161	56 (31-75)	110 (68)	142 (88)	19 (12)	29 (18)	132 (82)
FACS[59]	cis + irino	145	62 (30-74)	97 (67)	145 (100)	--	31 (21)	114 (79)
	carb + pac	145	63 (33-74)	99 (68)	145 (100)	--	28 (19)	117 (81)
	cis + gem	146	61 (34-74)	101 (69)	146 (100)	--	30 (21)	116 (79)
	cis + vin	145	61 (28-74)	101 (70)	145 (100)	--	26 (18)	119 (82)
Ferry *et al*. [60]	cis(80) + gem	456	63 (30-79)	286 (63)	--	35 (8)	146 (32)	310 (68)
	cis(50) + gem	454	63 (32-82)	291 (64)	--	34 (7)	145 (32)	309 (68)
	carb + gem	453	63 (29-83)	268 (59)	--	34 (8)	144 (32)	309 (68)
Gebbia *et al*, 2003[61]	cis + ifo + gem + vingi1	62	61 (48-71)	50 (81)	51 (82)	11 (18)	29 (47)	33 (53)
	cis + ifo + gem + vinvc1	60	59 (32-72)	45 (75)	51 (85)	9 (15)	29 (48)	31 (52)
	cis + vin	140	63 (36-72)	106 (76)	116 (83)	24 (17)	65 (46)	75 (54)
	cis + gem	138	60 (38-73)	108 (78)	111 (80)	27 (20)	64 (46)	74 (54)

Trial ID	Treatment	N randomised	Age	Male (%)	ECOG 0/1	ECOG 2	Stage IIIB (%)	Stage IV (%)
GFPC 99-01[62]	cis+ vin	49	56 (35-69)	41 (84)	43 (88)	6 (12)	2 (4)	47 (96)
	carb + gem	51	60 (44-69)	42 (82)	44 (86)	7 (14)	6 (12)	44 (86)
Helbekkmo *et al*, 2007[63]	carb + vin	218	67 (37-86)	128 (59)	156 (72)	62 (28)	65 (30)	153 (70)
	carb + gem	214	67 (37-85)	136 (64)	153 (71)	61 (29)	60 (28)	154 (72)
Kawahara *et al*, 2013[64]	carb + doc	60	67.5	43 (72)	60 (100)	0 (0)	24 (40)	36 (60)
	carb + pac	30	65.5	22 (73)	30 (100)	0 (0)	10 (33)	20 (67)
KEYNOTE-407[7, 8]	pembro + carb + nab/pac	278	65 (29-87)	220 (79)	--	--	--	--
	carb + nab/pac	281	65 (36-88)	235 (84)	--	--	--	--
Martoni *et al*, 2005[65]	cis + vin	137	62 (32-75)	104 (76)	49 (79)	13 (21)	26 (42)	36 (58)
	cis + gem	135	63 (33-77)	110 (81)	50 (86)	8 (14)	22 (38)	36 (62)
Mazzanti *et al*, 2003[66]	cis + gem	62	60 (40-75)	45 (73)	255 (83)	53 (17)	108 (35)	178 (58)
	carb + gem	58	65 (45-75)	49 (84)	256 (83)	53 (17)	90 (29)	191 (62)
Rosell *et al*, 2002 [67]	cis + pac	309	58 (29-78)	253 (82)	--	8 (22)	--	36 (100)
	carb + pac	309	58 (27-76)	258 (83)	--	11 (31)	--	35 (100)
Saad *et al*, 2017[42]	cis + gem	36	NA	26 (72)	194 (95)	--	--	167 (81)
	carb + gem	35	NA	29 (83)	184 (92)	--	--	164 (82)
Scagliotti *et al*, 2002[68]	cis + gem	205	63 (28-81)	167 (81)	185 (92)	--	--	163 (81)
	carb + pac	201	62 (30-77)	152 (76)	--	--	22 (11)	180 (89)
	cis + vin	201	63 (38-78)	157 (78)	--	--	24 (12)	182 (88)
SWOG [69]-9509	cis + vin	202	61 (32-83)	136 (67)	--	--	135 (33)	273 (67)
	carb + pac	206	62 (26-80)	144 (70)	--	--	132 (33)	274 (67)
TAX 326[70]	cis + doc	408	61 (30-81)	294 (72)	--	--	133 (33)	271 (67)
	carb + doc	406	59 (23-87)	292 (72)	377 (99)	1 (0)	38 (10)	341 (90)
	cis + vin	404	61 (35-80)	302 (75)	374 (99)	2 (1)	38 (10)	339 (90)
Treat *et al*, 2010[71]	carb + gem	379	64.1 (37-89)	221 (58)	375 (99)	1 (0)	40 (11)	339 (89)
	gem + pac	377	64.3 (33-91)	236 (63)	--	--	36 (41)	51 (59)
	carb + pac	379	64.1 (39-85)	231 (61)	--	--	34 (38)	55 (62)
Zatloukal *et al*, 2003[72]	cis + gem	87	63 (39-75)	67 (77)	ECOG 0/1	ECOG 2	Stage IIIB (%)	Stage IV (%)
	carb + gem	89	62 (46-76)	68 (76)	18 (53)	16 (47)	9 (26)	25 (74)

ECOG - Eastern Cooperative Oncology Group; cis - cisplatin; carb - carboplatin; gem - gemcitabine; pac - paclitaxel; nab/pac – nab-paclitaxel; doc - docetaxel; vin – vinorelbine; ifo – ifosfamide; irino - irinotecan

Seventeen trials were multicentre RCTs and three trials (Chang *et al*., 2008;[53] Chen *et al*., 2004;[54] Chen *et al*., 2007[55]) were either single centre studies or the number of study sites was not reported. Most studies were Phase II or Phase III trials. Blinding was either not reported or studies were open-label. Trials were published from 2001 and some were still ongoing. Of the trials conducted in only one country, nine were in European countries, two in the USA, two in Taiwan, two in Japan, and one in China. The study designs appear consistent with the NICE scope,[6] but only one of the studies included a UK centre (Ferry *et al*, 2017).[60] Most of the trials were conducted relatively recently. The included trials broadly represent best practice. Maintenance and second-line chemotherapy use was reported in some trials, although there is an absence of second-line immunotherapy in the trials as well as first line immunotherapy for patients with PD-L1 TPS≥ 50% (pembrolizumab monotherapy). Additionally, some of the chemotherapy regimens are not widely used in England.

Eligibility criteria employed within the 20 additional studies in NMA2 are outlined in CS Appendix D[11] (pages 96-97). The majority of trials included patients with an ECOG PS of 0-2. In most trials, patients had to be 18 years old or over and ten trials applied an age cut-off. Patients with Stage IIIB and IV disease were eligible. Comparability of baseline population characteristics for all trials included in the ITCs are summarised on pages 92-93 of CS Appendix D. The ERG notes the following issues in terms of baseline comparability. Those with an ECOG PS of 0-2 were eligible for inclusion in the majority of trials. An ECOG status of 2 is associated with frailty and a high rate of SAEs. By including patients with an ECOG status of 2, studies may have introduced bias in terms of increased AEs, although it appears that the number of patients with ECOG PS 2 was relatively evenly distributed across the arms of the trials. Four studies included exclusively Asian patients (Chang *et al*., 2008;[53] Chen *et al*., 2004;[54] FACS;[59] Kawahara *et al*., 2013[64]), which limits the generalisability of the findings to the patient population in England.

ITC2: Squamous and PD-L1 ≥50%

The CS[1] states that two trials were selected for inclusion in ITC2: KEYNOTE-042[49] and KEYNOTE-407.[7, 8] These trials were selected for inclusion in order to compare pembrolizumab combination therapy with pembrolizumab monotherapy in patients with squamous NSCLC and PD-L1 TPS ≥50%. KEYNOTE-407[7, 8] assessed pembrolizumab combination therapy and KEYNOTE-042[49] assessed pembrolizumab monotherapy. Carboplatin-based combination chemotherapy was the common comparator, but regimens differed between the trials. Whilst KEYNOTE-407[7, 8] was a triple-blinded RCT, KEYNOTE-042[49] was an open-label trial.

Table 6: Study and patient characteristics of RCTs included in ITC2 (adapted from Tables 24 and 25, CS Appendix D1.2.2)

Trial ID	Treatment	N randomised	Age (range)	Male (%)	ECOG 0/1	ECOG 2	Stage IIIB (%)	Stage IV (%)
KEYNOTE -407[7, 8]	pembro + carb + nab/pac	278	65 (29-87)	220 (79)	--	--	--	--
	carb + nab/pac	281	65 (36-88)	235 (84)	--	--	--	--
KEYNOTE -042[49]	Pembro	637	63 (25-89)	450 (71)	--	--	--	--
	carb + pac (or carb + pemetrexed for non-squamous histology)	637	63 (31-90)	452 (71)	--	--	--	--

ECOG - European Cooperative Oncology Group; pembro - pembrolizumab; carb - carboplatin; pac - paclitaxel; nab/pac - paclitaxel/nab-paclitaxel

The patient eligibility criteria for KEYNOTE-042[49] are outlined in CS Appendix D[11] (page 97). In KEYNOTE-042,[49] patients had to be 18 years of age or more, with Stage IIIB and IV disease and an ECOG PS of 0-1, whilst in KEYNOTE-407,[7, 8] only patients with Stage IV disease were eligible. Some baseline characteristics relating to these criteria were not reported in KEYNOTE-042.[49] Consequently, the ERG is unable to make a judgement on baseline comparability across arms for disease stage and ethnicity. Age was comparable across treatment arms and whilst ECOG PS at baseline was not reported, the trial eligibility criteria required ECOG PS of 0 or 1. Neither KEYNOTE-407[7, 8] or KEYNOTE-042[49] included any UK centres. KEYNOTE-042[49] also included non-squamous patients.

Intervention characteristics across ITC1 and ITC2

The intervention characteristics for all RCTs included in both indirect treatment comparisons (n=25) are listed in Table 23 of CS Appendix D.[11] Pembrolizumab dosing was consistent across studies, in line with the NICE scope,[6] and was appropriate for UK practice. The interventions in the comparator studies were gemcitabine, paclitaxel, nab-paclitaxel, vinorelbine, pemetrexed, ifosfamide, irinotecan and docetaxel in combination with either cisplatin or carboplatin. In the CS, the cisplatin dose ranged from 50-120mg in the combination therapy regimens (the recommended monotherapy dose), despite the recommendation that the licensed dose of cisplatin should be reduced to 20mg/m² or more once every 3 to 4 weeks if used in combination therapy. However, the ERG acknowledges that the dose of cisplatin in combination chemotherapy in usual practice in England varies and a dose of 75-80mg/m² is typical. Overall, the intervention characteristics were consistent with the NICE scope, although nab-paclitaxel is not used in England and was not listed as a comparator in the NICE scope. The dosing and method of administration of the comparators was broadly comparable to current practice in England. None of

the studies included in NMA1/ITC1 included information about any second-line therapy given; some trials included in NMA2/ITC1 reported second-line chemotherapy, but not second-line immunotherapy.

CS Appendix D[11] (Tables 26 and 25) reports OS and PFS (or time to progression [TTP]) outcome data for trials included in the ITC. These outcomes are consistent with those outlined in the NICE scope.[6] The CS does not report sufficient information about the methods for assessing outcomes in the ITC trials. Therefore, the ERG cannot make an assessment regarding comparability in the definition of the outcomes and median follow up time.

4.3.4 Quality assessment of studies included in the ITCs

The included trials were quality assessed using the Cochrane Risk of Bias tool. The methods used to perform quality assessment were detailed in CS Appendix D[11] (page 84), and appear appropriate. Full details of the quality assessment for each of the 36 originally included trials are also provided (CS Appendix D, Table 81, page 164). The conclusion drawn from the company's quality assessment was that a majority of trials were judged to be at a low risk of selection, attrition and reporting bias. The ERG has verified a proportion of the CS critical appraisal results and found the quality assessment rating from those assessed to have been carried out accurately. However, the ERG notes that in a number of the trials, reporting was incomplete, therefore the company's assertion of low risk of bias across the majority of trials is overstated.

4.4 Summary and critique of the network meta-analysis and indirect treatment comparison

A summary of the NMAs including the ITC conducted by the company is provided in Table 7. As discussed in Section 4.3, two separate analyses were conducted for synthesising OS and PFS evidence in the two population groups: PD-L1 unselected and PD-L1 strong expression (TPS≥50%). The company's rationale was that PD-L1 expression is a known treatment effect modifier (clarification response,[12] question A5).

For the PD-L1 unselected population, two separate NMAs were performed: NMA1 only included trials with squamous histology patients (5 trials) and NMA2 included trials with patients unselected for histology (36 trials). Within NMA1, two fixed effect models were used – one was based on constant HRs, whilst the other was based on time-varying HRs using Weibull, Gompertz and second-order fractional polynomial models with powers of 0 or 1. The fixed effect model was chosen because of limited data availability. NMA2 utilised a meta-regression model to estimate treatment effects in the squamous population. For OS in one trial, the company imputed the proportion of squamous patients using the mean of all trials reporting the proportion of squamous patients. For PFS, no imputation of the proportion of squamous patients was required. Similar to NMA1, evidence was synthesised

assuming constant HRs and then time-varying HRs. Both fixed effect and random effects analyses were performed.

During the clarification stage, the ERG queried the discrepancy between the NMA results used in the health economic model and the NMA1 and NMA2 results presented in the CS (clarification response,[12] question B9). In response, the company presented an additional NMA whereby combination regimens containing different platinum drug components (carboplatin or cisplatin) were combined. This analysis included trials with squamous histology patients and which included carboplatin or cisplatin in the SC combination chemotherapy regimen (3 trials). This additional analysis is subsequently referred to as "NMA3" in this ERG report. Within NMA3, two fixed effect models were used: one was based on constant HRs, whilst the other was based on time-varying HRs.

For the PD-L1 strong expression subgroup (TPS ≥50%), the KEYNOTE-407[7, 8] and KEYNOTE-042 trials were included in the ITC. The company's reason for excluding KEYNOTE-024[17] was that the number of eligible patients with squamous histology and who received paclitaxel plus carboplatin was small. Several criteria were applied to select the patients from both trials (KEYNOTE-407[7, 8] and KEYNOTE-042) before conducting the ITC:

- squamous and PD-L1 strong expression patients were selected
- from the control group, patients assigned to paclitaxel plus carboplatin from KEYNOTE-042 and to paclitaxel/nab-paclitaxel plus carboplatin from KEYNOTE-407[7, 8] were selected
- patients with overall cancer Stage III at screening were excluded from KEYNOTE-042
- patients with untreated brain metastases were excluded from KEYNOTE-407.[7, 8]

The inverse probability of treatment weighting (IPTW) approach was used to balance the following covariates: ECOG PS (0 vs. 1), smoking status (never vs. former/current), age, gender, baseline tumour size in the two trials before generating the relative treatment effect using a constant HR within each trial. The Bucher method[73] was used for the ITC to obtain the indirect treatment effect based on the estimated constant HRs within each trial.

Table 7: Summary of indirect treatment comparison analysis

Population	Histology	NMA/ITC method	Model	Studies included	Comparator	Used in economic model?
PD-L1 unselected	Squamous	NMA1 (Bayesian)	Fixed effect NMA based on constant HRs	KEYNOTE-407[7, 8] and 4 other RCTs	Carboplatin + paclitaxel/nab-paclitaxel Carboplatin + gemcitabine Cisplatin + gemcitabine Cisplatin + paclitaxel Cisplatin + docetaxel	No
			Fixed effect NMA based on time-varying HRs			No
	Squamous	NMA3* (Bayesian)	Fixed effect NMA based on constant HRs	KEYNOTE-407[7, 8] and 2 other RCTs	Carboplatin/cisplatin + paclitaxel/nab-paclitaxel Carboplatin/cisplatin + gemcitabine Carboplatin/cisplatin + docetaxel	Yes
			Fixed effect NMA based on time-varying HRs			No
	Unselected	NMA2 (Bayesian)	Fixed effect and random effects meta-regression based on constant HRs	KEYNOTE-407[7, 8] and 35 other RCTs	Carboplatin + paclitaxel/nab-paclitaxel Carboplatin + gemcitabine Carboplatin + vinorelbine Carboplatin + docetaxel Cisplatin + gemcitabine Cisplatin + paclitaxel Cisplatin + docetaxel Cisplatin + vinorelbine	No
			Fixed effect and random effects meta-regression based on time-varying HRs			No
PD-L1 strong expression, no overall cancer Stage III at screening, no untreated brain metastases	Squamous	IPTW and Bucher ITC (Frequentist)	Bucher ITC based on constant HRs	KEYNOTE-407[7, 8] and KEYNOTE-042	Carboplatin + paclitaxel/nab-paclitaxel Pembrolizumab monotherapy	Yes (subgroup analysis, PD-L1 TPS≥50%)

ITC - indirect treatment comparison; NMA - network meta-analysis; RCT - randomised control trial; IPTW - inverse probability of treatment weighting
** Additional analysis presented in clarification response B9, whereby regimens containing different platinum drugs were combined*

The results of NMA1 and NMA2 based on constant HRs for the PD-L1 unselected population group can be found in the Tables 33-38 of the CS.[1] The results of NMA1 and NMA2 using time-varying HRs can be found in the CS, Appendix D,[11] Tables 27, 29, 31, 33, 36, 38, 40, 42, 45, 47, 49, 51, 54, 56, 58, 61, 63, 65, 68, 70 and 72. The NMA3 results based on constant HRs used in the company's health economic model are presented in Table 8. For the time-varying NMA3 results, the estimated HRs were reported in a figure format (clarification response,[12] question B9).

Table 8: Results of fixed effect network meta-analysis based on constant hazard ratios and combining platinum regimes (NMA3)

Comparison	HR [95% CrI]
Overall survival	
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. platinum + paclitaxel/nab-paclitaxel	**0.64 [0.49, 0.84]**
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. cisplatin + docetaxel	**0.62 [0.41, 0.94]**
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. platinum + gemcitabine	0.77 [0.49, 1.19]
Platinum + gemcitabine vs. platinum + paclitaxel/nab-paclitaxel	0.83 [0.59, 1.17]
Platinum + gemcitabine vs. cisplatin + docetaxel	0.81 [0.58, 1.12]
Cisplatin + docetaxel vs. platinum + paclitaxel/nab-paclitaxel	1.03 [0.75, 1.42]
Progression-free survival	
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. platinum + paclitaxel/nab-paclitaxel	**0.56 [0.45, 0.70]**
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. cisplatin + docetaxel	**0.53 [0.36, 0.78]**
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs. platinum + gemcitabine	**0.63 [0.45, 0.89]**
Platinum + gemcitabine vs. platinum + paclitaxel/nab- paclitaxel	0.89 [0.68, 1.16]
Platinum + gemcitabine vs. cisplatin + docetaxel	0.85 [0.62, 1.15]
Cisplatin + docetaxel vs. platinum + paclitaxel/nab-paclitaxel	1.05 [0.78, 1.43]

CrI - credible interval
Note - bold indicates a statistically significant result

Overall, the constant HR NMA results suggest that pembrolizumab combination therapy is an effective treatment relative to some of the chemotherapy regimens in the PD-L1 unselected population. Depending on the chemotherapy regimen used, pembrolizumab combination therapy could be associated with a statistically significantly or numerically superior HR for both OS and PFS compared to the combination chemotherapy regimens. The time-varying hazard ratios NMA results suggest that

the treatment effects could be time-varying compared to some of the combination chemotherapy regimens, hence the constant HR NMA results should be interpreted with caution.

For the PD-L1 strong expression population (TSP ≥50%), including additional limiting criteria to exclude patients with overall cancer Stage III at screening and those with untreated brain metastases from both trials, the ITC analysis suggests that pembrolizumab combination therapy is numerically superior to pembrolizumab monotherapy for both OS and PFS (HR [95% CI]: OS - 0.97, [0.50, 1.89]; PFS 0.58 [0.33, 1.01]). The ITC HRs used in the economic model do not match these results; the ERG is unclear regarding the source of the values applied in the company's model; this issue is further discussed in Section 5.3.3.

The results for OS and PFS within each KEYNOTE trial with squamous histology and with PD-L1 TPS ≥50% (KEYNOTE-407,[7, 8] KEYNOTE-042[49] and KEYNOTE-024[17]) are presented in Table 9. The table also includes IPTW-adjusted results for KEYNOTE-407 and for KEYNOTE-042. The weighting resulted in more favourable results for pembrolizumab combination therapy for OS and PFS in KEYNOTE-407, and a less favourable result for pembrolizumab monotherapy for OS and the same point estimate for PFS in KEYNOTE-042.

Table 9: Within trial results for overall survival and progression-free survival (squamous histology and PD-L1 strong expression patient population)

	Unadjusted KEYNOTE-024[17] HR [95% CI]	**Unadjusted KEYNOTE-042[49] HR [95% CI]**	**Unadjusted KEYNOTE-407[7, 8] HR [95% CI]**	**Adjusted KEYNOTE-042[49] HR [95% CI]**	**Adjusted KEYNOTE-407[7, 8] HR [95% CI]**
Overall survival	[redacted]	[redacted]	0.64 [0.37, 1.10]	0.60 [0.41,0.88]	0.58 [0.33,1.00]
Progression-free survival	[redacted]	[redacted]	0.37 [0.24, 0.58]	0.61 [0.43,0.85]	0.35 [0.22,0.55]

CI - confidence interval

The ERG notes that the use of a fixed effect model in the NMAs and the Bucher approach in the ITC analysis underestimates the uncertainty in the treatment effect. The ERG also has concerns regarding the validity of the NMAs for the PD-L1 unselected population group. Firstly, KEYNOTE-407[7, 8] was the only trial included in the analyses which had a population in the chemotherapy arm which reflects current clinical practice in England, whereby some patients received second-line immunotherapy following disease progression. Secondly, some of the comparator trials included patients with ECOG PS 2. The clinical advisors to the ERG suggested that patients with ECOG PS 2 are likely to have different survival outcomes compared with patients with ECOG PS 0-1. The inclusion of these trials

without adjustment may lead to biased results. Finally, the clinical advisors to the ERG agreed that platinum-based regimens have very similar efficacy for the population of interest. This view was also supported by the company (clarification response,[12] question B11). In the same response, the company states that the NICE Appraisal Committee agreed with this view in TA411.[74] Assuming no difference in the treatment effect among the chemotherapy regimens, the comparator trials included in NMA1, NMA2, and NMA3 would be excluded from the NMAs as they would become single-arm studies.

For the second-order fractional polynomial model NMAs synthesising time-varying HRs, powers were set to be either 0 or 1. The company did not use negative powers as they led to unstable estimates of the HRs due to over-fitting the data (clarification response,[12] question A12). The ERG is unclear whether using negative powers would lead to an over-fitting problem, as the number of parameters remains the same regardless of the values for the power. The number of samples used in the burn-in period was not provided for the time-varying HRs analysis and the ERG speculates that unstable NMA results may be a result of the Markov chains not reaching convergence.

The company excluded KEYNOTE-024[17] from the ITC because "*the trial population of patients with squamous histology who received paclitaxel + carboplatin chemotherapy was very small (n=5 in each treatment arm)*" (clarification response,[12] question A21). The ERG notes that the published paper for KEYNOTE-024 reported that among the 27 squamous histology PD-L1 strong expression patients in the chemotherapy arm, 15 received carboplatin plus gemcitabine, five received carboplatin plus paclitaxel and seven received cisplatin plus gemcitabine.[75] The pembrolizumab monotherapy arm had 29 squamous histology PD-L1 strong expression patients (clarification response,[12] question A22). It is unclear why the CS[1] only considered patients who received carboplatin + paclitaxel and what "*each treatment arm*" referred to.

CS Appendix D[11] describes that IPTW was used to balance out the four treatment arms, including:

- KEYNOTE-407: pembrolizumab + chemotherapy arm,
- KEYNOTE-407: chemotherapy arm,
- KEYNOTE-042: pembrolizumab arm,
- KEYNOTE-042: chemotherapy arm.

The ERG is unclear whether the IPTW was conducted within each trial or across trials. The ERG was not able to check whether the baseline characteristics were well balanced after weighting, as the before and after weighting results on the standardised mean difference and variance ratio were presented across the four treatment arms, rather than within each trial.

Within each of the KEYNOTE trials (KEYNOTE-407,[7, 8] KEYNOTE-042[49] and KEYNOTE-024[17]), the before-weighting patient characteristics (including ECOG PS, smoking status, age, gender, baseline tumour size) were similar between the two treatment arms. Some small differences were observed for ECOG PS and baseline tumour size. In KEYNOTE-407,[7, 8] the pembrolizumab combination therapy arm had fewer patients with ECOG 0 but larger baseline tumour size than the chemotherapy arm (CS Appendix D,[11] Table 74). In KEYNOTE-042, the pembrolizumab monotherapy arm had smaller baseline tumour size than the chemotherapy arm (CS, Appendix D1.2.3.2 Table 74).[1] In KEYNOTE-024,[60] the pembrolizumab monotherapy arm had fewer patients with ECOG PS 0 and smaller baseline tumour size than the chemotherapy arm (clarification response,[12] question A20).

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG manually searched the clinicaltrials.gov website to confirm that no relevant trials had been missed. The ERG also replicated a CS search strategy to assess whether the number of citations generated was similar when the disease terms for the cost-effectiveness review were applied to the clinical review.

Due to the company's restriction to consider only RCTs, the ERG searched for non-RCT evidence including systematic reviews on evidence related to the safety of pembrolizumab combination therapy. The ERG conducted an additional targeted search in one database only (Medline) to ensure that no relevant drug safety data had been missed. The search was conceptualised from two perspectives:

(i) pembrolizumab AND adverse events AND relevant non-RCT study types (including case control, cohort, longitudinal, cross sectional, prospective, retrospective studies, observational studies and systematic reviews)

(ii) pembrolizumab AND adverse events AND lung or squamous cell cancers.

This dual approach to the search strategy intended to retrieve any evidence on AEs associated with pembrolizumab in other conditions (regardless of study type), and any non-RCT evidence in other types of cancer.

The ERG's search for non-RCT evidence resulted in 590 citations which were then sifted. No registered trials for post-marketing surveillance in the target population were identified; however, a number of relevant real-world studies, case reports and secondary data analyses of AEs in pembrolizumab for NSCLC were retrieved (discussed previously in Section 4.2.3).

The ERG performed additional ITC analyses to include squamous histology and PD-L1 strong expression patients from KEYNOTE-024.[17] The ERG's additional analyses used a Bayesian random effects NMA model.[76] An informative prior distribution proposed by Ren *et al*. (2018)[77] was used for

the heterogeneity parameter as there were few studies included in the network. This prior is a truncated Turner *et al*. (2012)[78] prior (a log normal (-2.56, 1.74^2)). The truncation is based on the judgement that the HR in one study would not be ≥10 times greater than in another.

The ERG's ITC results for both OS and PFS are presented in Table 10. In summary, there is no evidence to suggest there is a difference between pembrolizumab combination therapy and pembrolizumab monotherapy for both OS and PFS, but pembrolizumab combination therapy is associated with a numerically superior HR for PFS compared to pembrolizumab monotherapy. The analyses including unadjusted data from three KEYNOTE trials result in a less favourable treatment effect for both OS and PFS for pembrolizumab combination therapy compared with pembrolizumab monotherapy.

Table 10: ERG's ITC results

Pembrolizumab combination therapy vs. pembrolizumab monotherapy	**Hazard ratio Median [95% CrI]**	**Study included**	**Model**
Overall survival	0.96 [0.33, 2.80]	Adjusted KEYNOTE-407[7, 8] Adjusted KEYNOTE-042[49]	Random effects
	0.91 [0.36, 2.20]	Adjusted KEYNOTE-407[7, 8] Adjusted KEYNOTE-042[49] Unadjusted KEYNOTE-024[17]	Random effects
	1.09 [0.43, 2.68]	Unadjusted KEYNOTE-407[7, 8] Unadjusted KEYNOTE-042[49] Unadjusted KEYNOTE-024[17]	Random effects
Progression-free survival	0.57 [0.21,1.62]	Adjusted KEYNOTE-407[7, 8] Adjusted KEYNOTE-042[49]	Random effects
	0.62 [0.27, 1.51]	Adjusted KEYNOTE-407[7, 8] Adjusted KEYNOTE-042[49] Unadjusted KEYNOTE-024[17]	Random effects
	0.65 [0.29, 1.53]	Unadjusted KEYNOTE-407[7, 8] Unadjusted KEYNOTE-042[49] Unadjusted KEYNOTE-024[17]	Random effects

CrI - credible interval

4.6 Conclusions of the clinical effectiveness section

The ERG considers the KEYNOTE-407[7, 8] trial to be a high-quality RCT which is relevant to the decision problem. Whilst the study did not include any UK centres, the baseline characteristics of the trial population appear to reflect the target population in England. The comparator of carboplatin plus paclitaxel is valid for platinum-based combination chemotherapy and is consistent with the final NICE scope;[79] however, there was no pembrolizumab monotherapy comparator arm in the KEYNOTE-407 trial for those with strong PD-L1 expression (TPS ≥ 50%), as is used in current clinical practice in England. The clinical evidence regarding the efficacy of the intervention using the pre-specified outcomes of OS and PFS for this ongoing trial appears to be accurately reported within the CS.[1]

The results from IA2 of KEYNOTE-407 indicate that pembrolizumab combination therapy is statistically superior to carboplatin plus paclitaxel/nab-paclitaxel for OS, PFS and ORR. Improvements in OS and PFS were observed in all PD-L1 subgroups. The ERG highlights that the OS treatment effect in the pembrolizumab combination therapy arm may be contingent on chemotherapy as a potential treatment effect modifier as it potentially alters PD-L1 status. However, it is unknown whether and how other relevant chemotherapy comparators may alter PD-L1 expression and subsequently effect treatment response to pembrolizumab.

The trials included in the company's NMAs/ITCs for pembrolizumab combination therapy included trials which do not accurately reflect current clinical practice in England, whereby patients may receive second-line immunotherapy following disease progression and patients with strong PD-L1 expression are eligible for first-line pembrolizumab monotherapy. Additionally, some trials of comparators included in the NMA contained some patients with ECOG PS 2, and these patients were not eligible for KEYNOTE-407.[8] The company's ITC (adjusted) analyses trimmed the population; the unadjusted analysis does not trim the population, but potentially could be biased if it is believed that the baselines were not balanced.

Whilst the CS[1] concludes that pembrolizumab combination therapy has an acceptable tolerability profile, the ERG regards the company's safety analysis to reflect a 'light-touch' approach which does not include non-randomised evidence or meta-analyses; an NMA for AE outcomes has not been conducted by the company. Long-term data are lacking, which is of particular importance for PD-L1 drugs whereby IRAEs may occur with a delayed onset to those measured in the KEYNOTE-407 trial. Data from the final analysis of KEYNOTE-407 will help to reduce some of this uncertainty.

5 COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel for the first-line treatment of metastatic squamous NSCLC.

5.1 Company's review of published cost-effectiveness studies

The company undertook a systematic review to identify relevant cost-effectiveness studies from published literature and from previous NICE technology appraisals.

5.1.1 Company's search methods

A combined SLR was conducted to identify published studies of cost-effectiveness, HRQoL and cost/resource use. As noted in the critique of the clinical effectiveness review, a different approach was used to conceptualise disease terms for this search than that used in the clinical effectiveness review. The terms used here are more sensitive (i.e. they retrieve more references) but each version found unique results; therefore, maximum retrieval would have been achieved by using a combination of both sets of disease terms for each of the reviews.

A date limit was applied to restrict cost/resource use studies to those published since 2008. When this was queried by the ERG (clarification response,[12] question B3), the company's justification was that this was to intended to capture current clinical practice.

Terms for included study types were based on filters from expert sources, including ScHARR, although some modifications have been made. For example, a geographical filter was applied to the results from the cost/resource use search (CS Appendix G,[11] Table 1, page 190).

Given the limited time available within the STA process, it was not feasible for the ERG to re-run the searches, sifting and study selection with these errors corrected, hence their implications are unclear.

5.1.2 Eligibility criteria for the company's review of published economic evaluations

Whilst the eligibility criteria for the company's review allowed for the inclusion of studies which evaluated any comparator regimen, the criteria specifically defined the intervention as pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel (see CS,[1] Section B.3.1, page 126). As a consequence of this criterion, the company's searches did not identify any relevant economic studies for inclusion in the review.

Additional *ad hoc* searching undertaken by the ERG did not identify any relevant studies in the squamous NSCLC population published after the company's search cut-off date. On the basis of these searches, the ERG notes that a US-based economic analysis of first-line pembrolizumab plus chemotherapy and a platinum drug in patients with non-squamous NSCLC (funded by the company) was published shortly after this cut-off date.[80] This analysis uses a similar approach to the model submitted as part of the CS[1] regarding the use of external data from the US Surveillance Epidemiology and End Results (SEER) registry.[81] The ERG believes that none of the previous NICE technology appraisals of lung cancer treatments have involved the direct use of SEER data to inform the survival model parameters. The ERG considers the use of these data to estimate long-term survival outcomes to be problematic; this issue is discussed in more detail in Section 5.3.3.

5.2 Description of company's health economic analysis

This section provides a detailed description of the methods and results of the company's health economic analysis. The ERG notes that several sections of the CS[1] do not clearly report the analyses that have been done, hence some aspects of the model description presented here are instead reliant on scrutiny of the model formulae by the ERG. However, this is further complicated by a lack of correspondence between the CS and the implemented model and the presence of errors in the model. In addition, the sources of some of the model parameters values (e.g. risks of AEs and time on treatment for pembrolizumab monotherapy) are inconsistent between the CS and the model; this may negatively impact on the accuracy of the information presented throughout this chapter.

5.2.1 Model scope

As part of its submission to NICE,[1] the company submitted a fully executable health economic model programmed in Microsoft Excel®. The scope of the company's model is summarised in Table 11. The company's base case analyses assess the incremental cost-effectiveness of pembrolizumab in combination with carboplatin plus paclitaxel/nab-paclitaxel versus standard care (SC) chemotherapy (carboplatin/cisplatin in combination with chemotherapy) from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over a 30-year (lifetime) horizon. Cost-effectiveness is expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. Unit costs are valued at 2016/17 prices. Health outcomes and costs are discounted at a rate of 3.5% per annum. The CS[1] reports two sets of base case comparisons:

- **Base Case Analysis 1 (trial comparator).** This analysis compares pembrolizumab in combination with carboplatin plus paclitaxel/nab-paclitaxel versus carboplatin and paclitaxel/nab-paclitaxel, based on the KEYNOTE-407 trial[7, 8] and other external data.
- **Base Case Analysis 2 (NMA comparators).** This analysis compares pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel based on the KEYNOTE-407 trial[7,

[8] versus: (i) carboplatin/cisplatin plus docetaxel; (ii) carboplatin/cisplatin plus gemcitabine and (iii) carboplatin/cisplatin plus paclitaxel, based on the company's NMA for the squamous, metastatic PD-L1 unselected NSCLC population[12] and other external data. Within this analysis, the costs and health outcomes for the pembrolizumab group remain identical to those for Base Case Analysis 1. Outcomes for the comparator groups are based on hazard ratios (HRs) derived from the company's NMA3 (see Section 4.4); the corrected version of the company's model provided after clarification[82] applies these HRs to the pembrolizumab combination therapy group as a baseline. The comparator for Base Case Analysis 1 (carboplatin and paclitaxel/nab-paclitaxel) is not included in Base Case Analysis 2.

The CS[1] also reports cost-effectiveness results for three subgroups of patients defined by their level of PD-L1 expression (TPS <1%, TPS 1-49% and TPS ≥50%). Within each PD-L1 subgroup, pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel is compared against carboplatin and paclitaxel/nab-paclitaxel alone (SC chemotherapy), based on KEYNOTE-407[7, 8] (as per Base Case Analysis 1). In addition, within the PD-L1 TPS ≥50% subgroup, the CS presents a further indirect comparison of pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel versus pembrolizumab monotherapy, based on patient-level PFS and OS data from selected (partially matched) subsets of patients enrolled in KEYNOTE-407[7, 8] and KEYNOTE-042[49] (referred to as ITC2 in Chapter 4).

Table 11: Summary of company's model scope

Population	*Overall population (Base Case Analyses 1 and 2)* Patients with untreated squamous metastatic NSCLC, with additional characteristics as defined by the KEYNOTE-407 trial[7, 8] inclusion criteria (ECOG PS 0 or 1, no active, symptomatic, or clinically unstable CNS metastases, life expectancy >3 months). *Subgroup analyses by PD-L1 expression* • PD-L1 TPS <1% • PD-L1 TPS 1-49% • PD-L1 TPS ≥50%
Time horizon	30 years (lifetime)
Intervention	Pembrolizumab in combination with carboplatin plus paclitaxel/nab-paclitaxel
Comparator	*Overall population – Base Case Analysis 1 (trial comparator)* • Carboplatin plus paclitaxel/nab-paclitaxel *Overall population – Base Case Analysis 2 (NMA comparators)* • Carboplatin/cisplatin plus docetaxel • Carboplatin/cisplatin plus gemcitabine • Carboplatin/cisplatin plus paclitaxel *PD-L1 TPS <1% and TPS 1-49% subgroups* • Carboplatin plus paclitaxel/nab-paclitaxel *PD-L1 TPS ≥50% subgroup* • Carboplatin plus paclitaxel/nab-paclitaxel • Pembrolizumab monotherapy
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% for health outcomes and costs
Price year	2016/17

NSCLC - non-small-cell lung cancer; ECOG - Eastern Cooperative Oncology Group; PS - performance status; PD-L1 - programmed death-ligand 1; TPS - tumour proportion score; QALY - quality-adjusted life year; PSS - Personal Social Services; CNS - central nervous system; NMA - network meta-analysis

Population

The population within the company's base case analyses reflects the intention-to-treat (ITT) population of the KEYNOTE-407 trial[7, 8], that is, patients with untreated squamous metastatic NSCLC, with additional characteristics as defined by the inclusion criteria applied in the KEYNOTE-407 trial[7, 8] (ECOG PS 0 or 1, no active, symptomatic, or clinically unstable central nervous system (CNS) metastases, life expectancy >3 months). The CS[1] does not report the anticipated wording of the marketing authorisation for pembrolizumab combination therapy within the squamous metastatic NSCLC indication. Following a request for clarification from the ERG, the company stated that the proposed indication wording presented in the EMA regulatory submission for the squamous NSCLC indication relates to [redacted] (personal communication – MSD, 06/12/2018). The population included in the company's economic analysis is in line with the final NICE scope[6] and the anticipated marketing authorisation, although the

additional criteria regarding ECOG PS, CNS metastases and remaining life expectancy are not stated in either the population defined in the NICE scope or the anticipated marketing authorisation. The clinical advisors to the ERG noted that the use of pembrolizumab should be in line with the eligibility criteria applied in the KEYNOTE-407 trial.

Within the PD-L1 TPS ≥50% subgroup, the analysis excludes patients with untreated brain metastases; this population may be narrower than the patient population seen in clinical practice. It is unclear whether these patients would be eligible for treatment under the anticipated marketing authorisation in the untreated squamous NSCLC population. Clinical advisors to the ERG noted that in practice, patients with symptomatic or clinically unstable CNS metastases would not be offered treatment with pembrolizumab combination therapy.

Interventions and comparators

The intervention included in the company's model is pembrolizumab in combination with carboplatin plus paclitaxel/nab-paclitaxel (pembrolizumab combination therapy). This is in line with the final NICE scope[6] and the anticipated marketing authorisation for pembrolizumab in the first-line metastatic squamous NSCLC indication. Dosing and treatment schedules for the intervention and comparator groups assumed in the company's model are summarised in Table 12. All regimen components are administered via intravenous (IV) infusion. Pembrolizumab is assumed to be given at a dose of 200mg once every 3 weeks (Q3W) for a maximum of 35 doses (approximately 2 years of treatment). Paclitaxel is assumed to be given at a dose of 200mg/m^2, nab-paclitaxel is assumed to be given at a dose of 100mg/m^2 and carboplatin is assumed to be given at a dose of AUC 6 (mg/mL/min – target maximum dose). Platinum-based therapy and chemotherapy (excluding gemcitabine, which is given twice every 3 weeks [Q1.5W]) are each assumed to be administered once every 3 weeks (Q3W) for up to 4 cycles. Within the model, acquisition cost calculations are based on the mean body surface area (BSA) of patients recruited at the European centres in KEYNOTE-407,[7, 8] assuming a population mean value rather than a distribution.

Within the overall squamous PD-L1 unselected NSCLC population, the CS[1] includes pairwise comparisons of pembrolizumab combination therapy against the following regimens:

- Carboplatin plus paclitaxel/nab-paclitaxel (based on KEYNOTE-407[7, 8])
- Cisplatin/carboplatin plus docetaxel (based on the company's NMA [squamous, PD-L1 unselected])
- Cisplatin/carboplatin plus gemcitabine (based on the company's NMA [squamous, PD-L1 unselected])

- Cisplatin/carboplatin plus paclitaxel (based on the company's NMA [squamous, PD-L1 unselected])

Within the company's PD-1L subgroup analyses, the CS[1] includes pairwise comparisons of pembrolizumab combination therapy against the following treatment regimens:

- Carboplatin plus paclitaxel/nab-paclitaxel (PD-L1 TPS<1%, 1-49% and ≥50% subgroups, based on the KEYNOTE-407[7, 8] trial)
- Pembrolizumab monotherapy (PD-L1 TPS ≥50% subgroup only, based on an ITC between KEYNOTE-407[7, 8] and KEYNOTE-042[49]).

The final NICE scope[6] also includes vinorelbine in combination with a platinum drug as a comparator; this regimen is not included in the company's economic analyses due to a lack of relevant evidence (see clarification response,[12] question B11).

The model includes the costs of second-line therapy for all treatment groups. Within the SC chemotherapy comparator groups, the model includes the costs associated with the use of second-line immunotherapy, chemotherapy and platinum drugs. Within the pembrolizumab combination therapy group, the model includes costs associated with second-line chemotherapy and platinum drug regimens only. With the exception of the pembrolizumab monotherapy comparator group, these costs are based on the use of second-line treatments received in KEYNOTE-407.[7, 8] Issues surrounding these data are discussed in Section 5.3.3.

Table 12: Dosing and treatment schedules for first-line treatments included in the company's model*

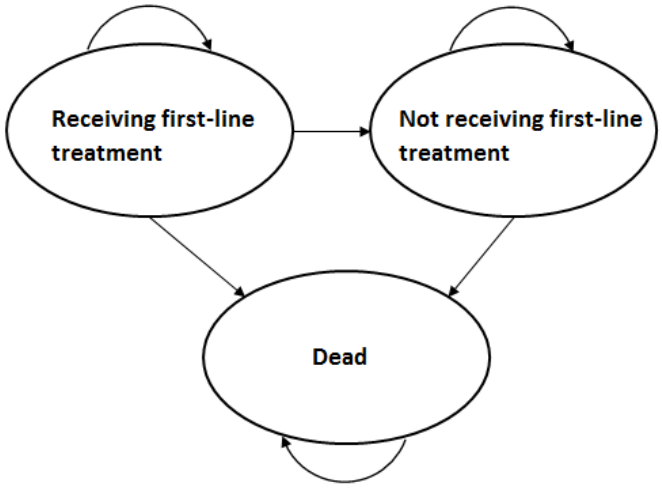
Population	Regimen	Regiment component	Administration route	Dosing schedule	Maximum treatment duration
Overall population and PD-L1 TPS <1%, 1-49% and ≥50% subgroups	Pembrolizumab + carboplatin + paclitaxel / nab-paclitaxel	Pembrolizumab	IV	200mg Q3W	35 cycles (approximately 2 years)
		Carboplatin	IV	AUC 6mg/mL/min Q3W	4 cycles (12 weeks)
		Paclitaxel	IV	200mg/m^2 Q3W	4 cycles (12 weeks)
		Nab-paclitaxel	IV	100mg/m^2 Q1W	4 cycles (12 weeks)
	Carboplatin + paclitaxel / nab-paclitaxel†	Carboplatin	IV	AUC 6mg/mL/min	4 cycles (12 weeks)
		Paclitaxel	IV	200mg/m^2 Q3W	4 cycles (12 weeks)
		Nab-paclitaxel	IV	100mg/m^2 Q1W	4 cycles (12 weeks)
Overall population only	Cisplatin/carboplatin + docetaxel	Cisplatin	IV	75mg/m^2 Q3W	4 cycles (12 weeks)
		Carboplatin	IV	400mg/m^2 Q3W	4 cycles (12 weeks)
		Docetaxel	IV	75mg/m^2 Q3W	4 cycles (12 weeks)
	Cisplatin/carboplatin + gemcitabine	Cisplatin	IV	75mg/m^2 Q3W	4 cycles (12 weeks)
		Carboplatin	IV	400mg/m^2 Q3W	4 cycles (12 weeks)
		Gemcitabine	IV	1,250 mg/m^2 Q1.5W	4 cycles (12 weeks)
	Cisplatin/carboplatin + paclitaxel	Cisplatin	IV	75mg/m^2 Q3W	4 cycles (12 weeks)
		Carboplatin	IV	400mg/m^2 Q3W	4 cycles (12 weeks)
		Docetaxel	IV	200mg/m^2 Q3W	4 cycles (12 weeks)
PD-L1 TPS ≥ 50% subgroup only	Pembrolizumab monotherapy	Pembrolizumab	IV	200mg Q3W	35 cycles (approximately 2 years)

AUC - area under the curve; IV - intravenous; PD-L1 - programmed death-ligand 1; Q1.5W - every 1.5 weeks; Q3W - every 3 weeks; TPS - tumour proportion score.
** Full details of comparator regimens are not included in the CS. The information presented here is taken from the company's model*
† KEYNOTE-407[7] comparator regimen includes placebo (normal saline IV infusion)

5.2.2 Model structure and logic

The CS[1] (page 132) describes the company's economic model as a partitioned survival model based on three health states: (1) progression-free; (2) progressed disease, and (3) dead. The ERG considers this interpretation of the company's implemented model to be misleading: whilst the model defines a partition between the alive health states in terms according to the presence/absence of progression, neither the costs nor health outcomes for any treatment strategy are influenced by progression status. The ERG considers that the company's implemented model is better described as a partitioned survival model based on three health states: (1) receiving first-line treatment; (2) not receiving first-line treatment (including second-line treatment for some patients), and (3) dead (see Figure 4). It should also be noted that this partition influences only the costs of the treatment options; health outcomes are modelled according to time-to-death rather than any explicit definition of the patient's underlying health status.

Figure 4: Company's model structure

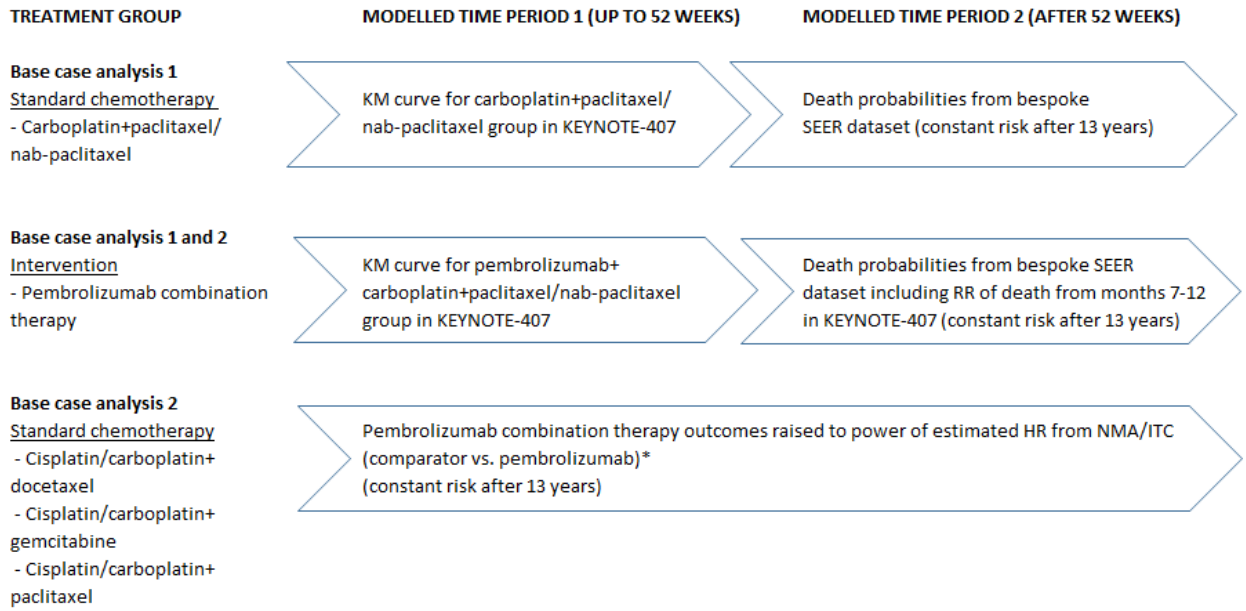


The model operates as follows. Patients enter the model and receive first-line treatment with pembrolizumab combination therapy or platinum-based combination chemotherapy (SC chemotherapy regimen defined according to the source of comparator data outcomes and subgroup, see Table 11). Following discontinuation of first-line therapy, a proportion of surviving patients go on to receive second-line therapy. The risk of death and HRQoL are assumed to be independent of patients' modelled health state.

OS is modelled using a piecewise approach (see Figure 5). Within the comparator group for Base Case Analysis 1, the probability of being alive is determined by the observed KM curve for OS from the KEYNOTE-407 trial[7, 8] up to week 52; beyond this timepoint, the conditional probability of survival in each model cycle is based on a bespoke analysis of data from the US SEER registry.[81] An additional

mortality constraint is also applied to ensure that the probability of survival for the modelled NSCLC population does not exceed that of the general population of England. Within the pembrolizumab combination therapy group, the effect of treatment on OS is modelled by: (i) using the intervention group KM curve from KEYNOTE-407 up to 52 weeks, and (ii) after 52 weeks, applying a constant relative risk (RR) of death (based on a comparison of OS events between treatment groups during months 7-12 in KEYNOTE-407) to the annual SEER OS probabilities for all subsequent model cycles.

Figure 5: Company's approach for modelling overall survival



** The company's application of the HRs from the NMA and ITC within the model is subject to errors - the figure reflects the approach adopted in the company's corrected model submitted following the clarification process (see Section 5.3.3)*

PFS is also modelled using a piecewise approach. Up to 26 weeks, the probability of being alive and progression-free is modelled using the observed KM curves for each treatment group from KEYNOTE-407.[7, 8] Beyond this timepoint, PFS is modelled using parametric (log normal) survivor functions fitted to the observed KM curves for PFS from KEYNOTE-407 using data from week 26 onwards (referred to as a 26-week cut-point). Separate parametric models were fitted to the PFS data for each treatment group, excluding a treatment-indicating covariate. As noted above, PFS has no bearing on the incremental cost-effectiveness ratio (ICER) for pembrolizumab combination therapy, except in one of the company's scenario analyses (see Table 29, company's scenario analysis 7b).

Within Base Case Analysis 2, the health outcomes and costs for the pembrolizumab combination therapy group are assumed to be the same as those for Base Case Analysis 1. In the corrected version of the company's model submitted following the clarification process, PFS and OS outcomes for the

SC chemotherapy comparators are modelled by applying HRs obtained from the company's NMAs to the intervention group PFS and OS curves.

The probability of being in the post-progression state at any time *t* is calculated as the difference between the cumulative survival probabilities for OS and PFS. The model includes the costs associated with second-line treatments; these costs are assumed to be incurred at the point of discontinuation of first-line therapy, rather than at the point of progression.

The model is evaluated using 1-week cycles. Costs and health outcomes evaluated over a total of 1,565 cycles (approximately 30 years). Half-cycle correction is applied to account for the timing of events.

HRQoL is determined largely by the patient's time to death, based on four categorical groups (<30 days; ≥30 to 180 days; ≥180 to 360 days, and ≥360 days). Health utilities are adjusted by age. The model also includes QALY losses associated with Grade 3-5 AEs based on the first-line treatment received; these are applied as a once-only decrement during the first model cycle.

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) disease management; (iv) second-line treatment; (v) management of AEs and (vi) end-of-life (terminal care) costs.

Drug acquisition and administration costs for each regimen are modelled as a function of the planned treatment schedule, the proportionate use of each regimen component (the mix of paclitaxel and nab-paclitaxel or cisplatin and carboplatin), time to treatment discontinuation (TTD), relative dose intensity (RDI) and unit costs. Disease management costs are assumed to include outpatient visits, clinical visits from general practitioners (GPs), nurses and therapists, examinations and tests; lower costs (based on patients being progression-free) are applied to patients whilst receiving first-line treatment and indefinitely for those who receive second-line treatment, whilst higher costs (based on patients with progressed disease) are applied to the remainder. Drug acquisition and administration costs for second-line treatment are applied at the point of discontinuation of first-line therapy based on the proportion of patients who received subsequent therapies by the IA2 of KEYNOTE-407;[7, 8] the use of subsequent immunotherapy (pembrolizumab or nivolumab) is included only for the comparator groups (those options in which pembrolizumab is not given first-line). AE management costs are applied as once-only costs during the first model cycle. End-of-life costs are applied as once-only costs at the point of death. The costs of PD-L1 testing are not included in the company's economic analysis. The analysis includes a price discount for pembrolizumab as part of its company's existing CAA.

5.2.3 Key assumptions employed in the company's model

The company's model employs the following key assumptions:

- All patients with untreated squamous metastatic NSCLC (within the anticipated licensed population) are assumed to be eligible for treatment with pembrolizumab, irrespective of PD-L1 expression. This includes those patients with PD-L1≥50%, who would be eligible for pembrolizumab monotherapy according to NICE TA531.[83]
- Within Base Case Analysis 1, the probability of PFS for patients in each treatment group is modelled using the observed time-to-event data from the first 26 weeks of KEYNOTE-407;[7, 8] beyond this timepoint, PFS in each treatment group is modelled using log normal models fitted to the post-26 week data from the trial.
- Within Base Case Analysis 2, PFS for the SC chemotherapy comparator group is modelled using HRs from the company's squamous NMA for PFS applied to the cumulative PFS probabilities for the pembrolizumab combination therapy group.
- With the exception of the company's scenario analyses around alternative utility values (see Table 29, company's scenario analysis 7b) the presence/absence of disease progression has no impact on the costs or health outcomes associated with any treatment option.
- Within Base Case Analysis 1, the probability of OS for patients receiving SC chemotherapy is modelled using the observed time-to-event data from the first 52 weeks of KEYNOTE-407;[7, 8] beyond this timepoint, OS is modelled using a bespoke dataset from the US SEER programme (relating to the period 1992 to 2014). A constant mortality risk is applied beyond 13 years; this is analogous to an assumption that OS follows an exponential distribution beyond this timepoint.
- The impact of pembrolizumab combination therapy on OS is modelled by: (i) using the observed time-to-event data from the first 52 weeks of KEYNOTE-407,[7, 8] and (ii) applying an RR derived from an analysis of OS outcomes during months 7-12 of KEYNOTE-407[7, 8] to the annual OS probabilities for the SC chemotherapy comparator group. This treatment effect is assumed to apply indefinitely; the model does not assume any loss of treatment effect on OS during treatment with or after discontinuation of pembrolizumab combination therapy.
- Within Base Case Analysis 2, OS outcomes for the SC chemotherapy comparator groups are modelled using HRs derived from the company's NMA. The ERG believes that the company intended to apply these HRs to the pembrolizumab combination therapy group; however, this analysis was subject to errors which were corrected following the clarification process.[82] These errors are discussed in Section 5.3.3.
- The model includes a general population mortality constraint to ensure that the risk of death for patients with NSCLC is never lower than that for the general population.

- TTD for pembrolizumab combination therapy is modelled using a generalised gamma function fitted to the observed time-to-event data from KEYNOTE-407;[7, 8] this function is truncated at 2 years to reflect the maximum treatment duration for pembrolizumab. TTD for the SC chemotherapy comparator groups (in both Base Case Analyses 1 and 2) is based on the observed KM curve from KEYNOTE-407 (maximum duration = 4 cycles [12 weeks]).
- Base Case Analysis 1 assumes a weighted cost of paclitaxel and nab-paclitaxel (used in combination with carboplatin), based on data from KEYNOTE-407.[7, 8] The CS notes that nab-paclitaxel is not available in England for this group of patients.
- The proportions of patients who receive second-line treatment and the mix of regimens received are assumed to be dependent on the first-line treatment received, and are based on the use of second-line therapies used in KEYNOTE-407.[7, 8] These are modelled as once-only costs.
- Patients who receive pembrolizumab combination therapy as first-line treatment are assumed not to be eligible for second-line treatment with further immunotherapy; these patients are instead assumed to be treated with SC chemotherapy (gemcitabine, paclitaxel, docetaxel, gemcitabine or vinorelbine) with or without a platinum drug (carboplatin or cisplatin).
- A proportion of patients who receive SC chemotherapy including a platinum drug as first-line treatment (i.e. not pembrolizumab) are assumed to receive second-line treatment using immunotherapy (pembrolizumab monotherapy or nivolumab monotherapy). A further proportion of patients are assumed to receive SC chemotherapy (gemcitabine, paclitaxel, docetaxel, gemcitabine or vinorelbine) with or without a platinum drug (carboplatin or cisplatin). Clinical advisors to the ERG noted that in practice, atezolizumab may also be offered as second-line treatment, and that docetaxel may be reserved for third-line treatment; as such, there are some differences between those treatments available in the trial and those used in usual clinical practice.
- HRQoL is modelled according to the patients' time to death rather than the presence/absence of disease progression.
- Only Grade 3-5 AEs occurring in ≥5% patients in one or both treatment groups are included in the company's model. These AEs are assumed to impact on both HRQoL and costs. The ERG notes that as data on AEs were collected up to 30 days and SAEs up to 90 days after the last dose of study medication, these may also include events relating to second-line treatments.
- Health utilities are age-adjusted based on general population norms.
- QALY losses and costs associated with AEs are applied only in the first model cycle, assuming a mean duration of [redacted] days.

5.2.4 Evidence used to inform the company's model parameters

Table 13 summarises the evidence sources used to inform the model's parameters in the company's base case analyses. These are discussed in detail in the subsequent sections. Additional model parameters and evidence sources used in the company's subgroup analyses are described in Section 5.2.5.

Table 13: Summary of evidence used to inform the company's base case analyses

Parameter group	Source
Patient characteristics (age, BSA, weight)	Based on characteristics of trial participants enrolled at European sites in KEYNOTE-407.[7, 8]
PFS - carboplatin+paclitaxel/nab-paclitaxel	Observed comparator group KM function for first 26 weeks followed by log normal model fitted to post-26-week data from KEYNOTE-407.[7, 8]
PFS - pembrolizumab combination therapy	Observed intervention group KM function for first 26 weeks followed by log normal model fitted to post-26-week data from KEYNOTE-407.[7, 8]
OS - carboplatin+paclitaxel/nab-paclitaxel	Observed comparator group KM function for first 52 weeks from KEYNOTE-407;[7, 8] after 52 weeks, mortality is modelled using data from SEER.[81] A constant mortality rate is assumed beyond 13 years. Modelled OS is constrained by general population mortality risk.
OS - pembrolizumab combination therapy	Observed intervention group KM function for first 52 weeks from KEYNOTE-407;[7, 8] after 52 weeks, mortality is modelled using data from SEER,[81] adjusted using an RR for death derived from data for months 7-12 in KEYNOTE-407.[7, 8] A constant mortality rate is assumed beyond 13 years. Modelled OS is constrained by general population mortality risk.
Mortality - general population	Derived from interim life tables for England.[84]
HRs for PFS - platinum drug plus docetaxel, gemcitabine or paclitaxel versus pembrolizumab combination therapy	Company's NMA (squamous, PD-L1 unselected).[12]
HRs for OS - platinum drug plus docetaxel, gemcitabine or paclitaxel versus pembrolizumab combination therapy	Company's NMA (squamous, PD-L1 unselected).[12]
TTD - pembrolizumab combination therapy	Generalised gamma model fitted to observed TTD data from KEYNOTE-407[7, 8] (truncated at 2 years).
TTD - SC chemotherapy	Observed KM curve for TTD from KEYNOTE-407[7, 8] (truncated at 12 weeks)
HRQoL	EQ-5D-3L data collected in KEYNOTE-407.[7, 8] Data analysed according to time to death (≥360 days, 180-360 days, 30-180 days and <30 days).
QALY loss resulting from AEs	EQ-5D-3L data collected in KEYNOTE-407[7, 8] (progression-free patients only). Disutility applied equally to all included AEs for a mean duration of [redacted] days.
Probability of receiving second-line therapy	Based on KEYNOTE-407.[7, 8]
Duration of second-line therapy	KEYNOTE-407.[7, 8]
Drug acquisition costs	Commercial Medicines Unit (CMU) Electronic Market Information Tool (eMIT)[85] and British National Formulary (BNF).[86]
Drug administration costs	NHS Reference Costs 2016/17.[8, 87]

Parameter group	Source
RDI	Based on KEYNOTE-407.[7, 8]
Disease management costs	Various sources including Brown *et al*[88] and NHS Reference Costs 2016/17[87]
Costs associated with AEs	Based on Brown *et al*,[88] previous NICE TAs,[74, 89-96] NHS Reference Costs 2016/17[87] and additional assumptions.[1]

AE - adverse event; BSA - body surface area; EQ-5D-3L - Euroqol EQ-5D 3-level; HR - hazard ratio; HRQoL - health-related quality of life; NMA - network meta-analysis; OS - overall survival; PD-L1 - programmed death-ligand 1; PFS - progression-free survival; QALY - quality-adjusted life year; TTD - time to treatment discontinuation

Initial patient characteristics at model entry

The model assumes an initial starting age of 65 years, a mean weight of [redacted] and a BSA of [redacted]; these characteristics reflect those of trial participants enrolled at European sites within KEYNOTE-407.[7, 8] All patient characteristics are applied as population mean values rather than using distributions.

Time-to-event parameters

Overall survival

The company's model adopts a piecewise approach for OS. The model uses the observed OS data from each arm of KEYNOTE-407[7, 8] up to a defined cut-point followed by the use of external data from SEER[81] thereafter, with an additional relative treatment effect applied for the pembrolizumab combination therapy group. This approach was adopted because the company's earlier attempts to apply piecewise parametric models using the KEYNOTE-407 data[7, 8] with a cut-point of 19 weeks produced *"potentially clinically implausible OS results for the SoC [standard of care] arm of 1-2% at 5 years"* (CS,[1] page 138). The CS argues that the predictions of the conventional parametric models were implausible due to the availability of immunotherapy as second-line therapy in England. CS Appendix L[11] provides more detail on these analyses, including goodness-of-fit statistics using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) (see Appendix 1), cumulative hazard plots and plots of the modelled survivor functions for OS. However, these parametric models are not used in the company's base case analyses and only two alternative parametric models - the exponential and log logistic function using a 19-week cut-point - are applied in the company's sensitivity analyses (see Table 29, company's scenario analyses 1a and 1b).

Within the company's Base Case Analysis 1, OS for the SC chemotherapy group is modelled using the observed KM function for the first 52 weeks. Beyond this timepoint, OS is modelled using death probabilities obtained from a bespoke analysis of the SEER database (data shown in Table 14). The bespoke SEER dataset[81] relates to US patients with metastatic squamous NSCLC who were diagnosed during the years 1992-2014.[1] The dataset started 2 months from the date of the patients' diagnosis to reflect the population enrolled into KEYNOTE-407.[7, 8] Different cohorts from SEER were used to estimate annual mortality risks for different time intervals: data from the period 2010-2014 were used to assess survival during years 1-5 of follow-up, data from 2000-2014 were used for years 6-10 of follow-up and data from 1992-2014 were used for years 11-13 of follow-up. No information is presented

in the CS[1] regarding why different SEER datasets were used for these three periods in the model or whether the three SEER cohorts were similar. As the SEER dataset had a maximum of 13 years follow-up, the annual mortality probability from SEER in year 13 was applied to all subsequent years in the company's model; this is equivalent to assuming an exponential OS model from this timepoint. Within the pembrolizumab combination therapy group of the model, a constant RR of death is applied to the SEER death probabilities; this treatment effect estimate was obtained from a comparison of death events between the treatment arms of KEYNOTE-407[7, 8] from months 7-12. This RR is applied to the annual mortality risk from SEER; the adjusted annual mortality probability is then converted to a weekly probability of death in each treatment group using standard methods for adjusting cycle duration[97] (assuming constant event risk in each period). In both treatment groups, the modelled survivor functions are further adjusted using life tables to ensure that the probability of death in the modelled cohort is never lower than that of the general population. The ERG notes that this constraint applies within both treatment groups, albeit at different timepoints, and is analogous to an implicit assumption of cure (see Section 5.3.3). As shown in Table 14, the risk of death for patients in the pembrolizumab combination therapy group is assumed to continue indefinitely despite the relatively short duration of pembrolizumab treatment (maximum duration = 2 years, RR of death applied to every weekly model cycle from year 2 onwards).

Table 14: SEER data, treatment effects and cycle conversion applied in the company's model

Year	Annual probability death – SC chemotherapy	Annual probability with pembrolizumab combination therapy (RR adjusted)	Weekly probability death – SC chemotherapy	Weekly probability death – pembrolizumab combination therapy
2	0.5427	0.3130	0.0149	0.0072
3	0.4118	0.2375	0.0101	0.0052
4	0.2253	0.1299	0.0049	0.0027
5	0.2189	0.1262	0.0047	0.0026
6	0.1972	0.1137	0.0042	0.0023
7	0.1638	0.0945	0.0034	0.0019
8	0.1598	0.0921	0.0033	0.0019
9	0.1288	0.0743	0.0026	0.0015
10	0.1191	0.0687	0.0024	0.0014
11	0.1692	0.0976	0.0035	0.0020
12	0.0795	0.0458	0.0016	0.0009
13+	0.0985	0.0568	0.0020	0.0011

RR – risk ratio

Figure 6 and Figure 7 present the modelled survivor functions for pembrolizumab combination therapy and carboplatin plus paclitaxel/nab-paclitaxel based on the company's piecewise KEYNOTE-407[7]/SEER[81] model, together with a comparison against the company's fitted piecewise parametric models using data from KEYNOTE-407[7, 8] assuming a 19-week cut-point.

Figure 6: Modelled OS functions estimated using Kaplan-Meier/SEER and piecewise parametric curve-fitting approaches, pembrolizumab combination therapy group in KEYNOTE-407 – figure redacted due to AiC

Figure 7: Modelled OS functions estimated using Kaplan-Meier/SEER and piecewise parametric curve-fitting approaches, SC chemotherapy group in KEYNOTE-407

***figure redacted due to AiC**

With respect to the SC chemotherapy comparator groups in Base Case Analysis 2 (carboplatin/cisplatin plus docetaxel, gemcitabine or paclitaxel), OS is modelled using HRs from the company's NMA.[12] The modelled survivor functions for all treatments included in the company's base case analyses are presented in Figure 8. The methods by which the company estimated cumulative OS probabilities for the NMA comparators in the model were not described in the CS.[1] Given that the HRs applied in the model are greater than 1.0, this would indicate that these were intended to be applied to the pembrolizumab combination therapy group as a baseline (by raising the cumulative OS probabilities to the power of the HR). This is the approach taken to apply relative treatment effects for PFS in the company's model. However, the calculations used to apply OS treatment effects in the company's original submitted model are unusual and use modelled projections from the trial comparator group rather than the intervention group. The ERG believes that this aspect of the company's model is subject to errors which invalidate the results of Base Case Analysis 2; the curves presented in Figure 8 which use functions from the company's original submitted model (prior to correction), should therefore be interpreted with caution. These errors are described in detail in Section 5.3.3.

Figure 8: Modelled OS functions for all treatment options included in company's base case analyses (includes general population mortality constraint)*†

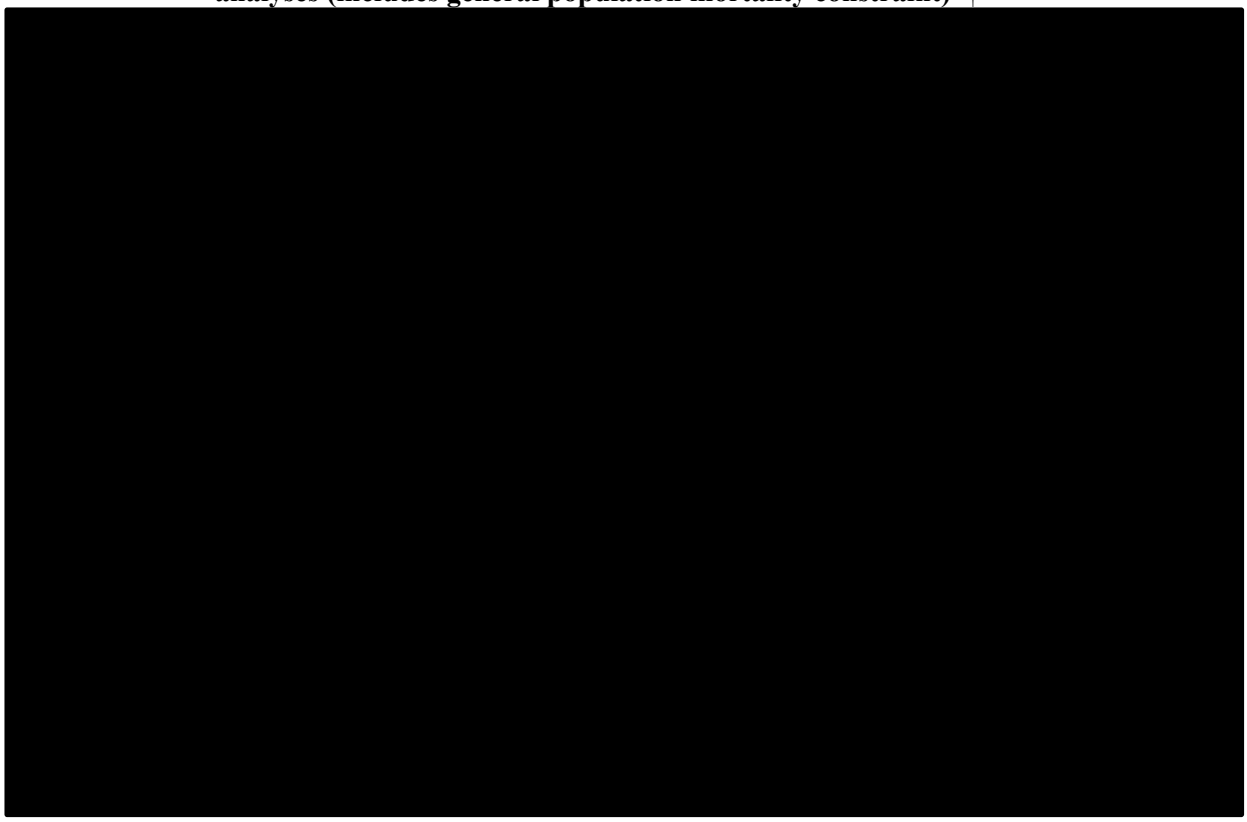


**figure redacted due to AiC*
** Survivor functions for the NMA comparator groups are subject to programming errors and are therefore incorrect*
† Note - the modelled OS function for carboplatin/cisplatin+paclitaxel is almost identical to the OS function for carboplatin+paclitaxel/nab-paclitaxel

PFS

The company's model also adopts a piecewise approach for PFS. The decision to adopt this approach was taken on the basis that the PFS curves for the treatment arms in KEYNOTE-407[7, 8] overlapped during the first 6 weeks.[11] According to CS Appendix L,[11] this *"did not allow the fitting of a full parametric curve."* Within Base Case Analysis 1, PFS for both treatment groups is modelled using the observed KM function up to 26 weeks, and using a log normal function fitted to the post-26 week data from KEYNOTE-407[7, 8] thereafter. The decision to use a 26-week cut-point was made based on the results of Chow tests and examination of the cumulative hazard functions for PFS. The use of alternative data cut-points of 16 weeks and 36 weeks and one alternative parametric model form (the generalised gamma function, 26-week cut-point) was explored in the company's scenario analyses (see Table 29).

Table 15 presents the AIC and BIC statistics for the company's fitted parametric models for PFS using alternative data cut-points; the best-fitting models are highlighted in bold. Figure 9 and Figure 10 present the modelled PFS survivor functions using the piecewise parametric models for the pembrolizumab combination therapy and SC chemotherapy groups, respectively.

Table 15: AIC and BIC statistics for company's piecewise parametric models for PFS

Week 16 cut-point				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Week 26 cut-point (base case)				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Week 36 cut-point				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; SC - standard care.
Best fitting models (lowest AIC/BIC) presented in bold

Figure 9: Modelled PFS functions using company's piecewise parametric curve-fitting approach, pembrolizumab combination therapy group in KEYNOTE-407, week 26 cut-point – Figure redacted due to AiC

Figure 10: Modelled PFS functions using company's piecewise parametric curve-fitting approach, SC chemotherapy group in KEYNOTE-407, week 26 cut-point – Figure redacted due to AiC

Within Base Case Analysis 2, the PFS functions for the SC chemotherapy options were modelled by applying an HR from the NMA to the cumulative PFS probabilities for the pembrolizumab combination therapy group in each cycle. Unlike the approach used to model OS, this was implemented by raising the cumulative PFS probabilities in the pembrolizumab combination therapy group to the power of the HR obtained from the NMA. Figure 11 presents the PFS functions for all treatment options included in the company's base case analyses. As shown in the figure, there is little difference in terms of PFS between any of the SC chemotherapy comparators; according to the company's model, pembrolizumab combination therapy is assumed to offer a considerable PFS advantage over existing treatments and a small proportion of patients (~2%) are assumed to remain alive and progression-free at 30-years. However, as noted in Section 5.2.2, the patient's progression status has no bearing on the ICER within the company's base case analyses.

Figure 11: Modelled PFS functions for all treatment options included in company's base case analyses, week 26 cut-point (includes general population constraint)

**Figure redacted due to AiC*

Time to treatment discontinuation (TTD)

The TTD data from KEYNOTE-407[7, 8] include both treatment discontinuation and death whilst on treatment as events (clarification response,[12] question B26). The company's model uses different approaches for modelling TTD depending on the treatment group under consideration. Within the base case analyses, TTD was modelled using data from KEYNOTE-407.[7, 8]

The company fitted standard parametric models (exponential, Weibull, log normal, log logistic, Gompertz and generalised gamma distributions) to the observed TTD data for the pembrolizumab combination therapy group from KEYNOTE-407[7, 8] (maximum follow-up of 77.86 weeks, Figure 12). The CS[1] notes that "*an estimated 16% of patients were still on pembrolizumab combination treatment as of the longest available follow-up time as of the cutoff date (April 2018)*". The generalised gamma distribution was selected for use in the company's base case analyses based on its AIC and BIC combined with visual inspection (CS Appendix N,[11] page 350); the ERG notes that the exponential model had a lower BIC than the generalised gamma (see Table 16). Within the model, TTD for pembrolizumab combination therapy is truncated at 2 years to reflect the maximum treatment duration.

Within the SC chemotherapy group, TTD is modelled using the KM curve from KEYNOTE-407[7, 8] directly; parametric curves were not required as the maximum treatment duration for chemotherapy is 12 weeks (4 treatment cycles). TTD for the NMA comparators was assumed to be the same as that for the carboplatin plus paclitaxel/nab-paclitaxel group in KEYNOTE-407.[7, 8]

Table 16: AIC and BIC statistics for company's parametric curve-fitting for TTD within the overall population of KEYNOTE-407[7, 8]

Model	Pembrolizumab combination		SC chemotherapy	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	N/a	N/a
Weibull	[redacted]	[redacted]	N/a	N/a
Log normal	[redacted]	[redacted]	N/a	N/a
Log logistic	[redacted]	[redacted]	N/a	N/a
Gompertz	[redacted]	[redacted]	N/a	N/a
Generalised gamma	[redacted]	[redacted]	N/a	N/a

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; SC - standard care; N/a - not applicable
**Best fitting models (lowest AIC/BIC) presented in bold*

Figure 12: Modelled TTD functions, pembrolizumab combination therapy group in KEYNOTE-407 – Figure redacted due to AiC

Figure 13 summarises the TTD functions for all options included in the company's base case analyses.

Figure 13: Modelled TTD functions for all treatment options included in company's base case analyses – Figure redacted due to AiC

Health-related quality of life

The KEYNOTE-407[8] trial included the measurement of HRQoL using the EQ-5D-3L questionnaire.[7] Within the trial, the EQ-5D-3L was administered at baseline and every 3 weeks until week 18, then every 9 weeks whilst patients were on treatment, for up to 48 weeks; in the case of treatment discontinuation, the questionnaire was also applied at the 30-day post-treatment safety follow-up visit.[1] The CS[1] is somewhat ambiguous regarding which HRQoL instrument was used to determine health utilities in the company's model. Specifically, page 73 of the CS states that the EQ-5D VAS was used to characterise utility values for the model; the ERG notes that this is not a preference-based instrument. In response to a request for clarification from the ERG[12] (question B6), the company stated that the EQ-5D-3L questionnaire was used. The ERG cannot verify this because the CSR[7] does not report any results from the EQ-5D-3L questionnaire.

In contrast to the majority of previous economic evaluations of cancer therapies, the company's base case analyses assume that HRQoL is dependent on the patients' time to death rather than the presence/absence of disease progression; the use of pre- and post-progression utility values is considered in the company's scenario analyses only (see Table 29). Within the company's base case analyses, time to death is defined in terms of four categories: <30 days to death and ≥30 days to 180; ≥180 to 360 days, and ≥360 days. The CS[1] (page 133) states that this approach is intended to reflect capture patients' HRQoL "*as a function of how much lifetime patients had left until they eventually died as predicted in the model.*" The CS also states that utilities defined by progression status in KEYNOTE-407[7, 8] do not show a large difference between the states due to the use of subsequent-line immunotherapy in the comparator arm and due to limitations in data collection for patients with progressed disease (see CS,[1] page 163). The CS does not provide any details regarding how the utility values for each time-to-death category were estimated from the trial data (i.e. if a statistical model was used or whether the utilities reflect the raw data). The utilities for each time-to-death category are assumed to be the same for the SC chemotherapy and pembrolizumab combination therapy groups; however, different utility values are applied for the pembrolizumab monotherapy comparator included in the company's subgroup analyses (see Section 5.2.5, Table 22). The CS does not provide justification for this approach.

Within the model, the proportion of patients in the time-to-death categories at each time *t* were calculated as follows:

- < 30 days from death – calculated as the probability of dying during the interval *t*+0 cycles and *t*+3 cycles;
- ≥30 days to 180 days from death – calculated as the probability of dying during the interval *t*+4 cycles and *t*+25 cycles;

- ≥180 to 360 days from death – calculated as the probability of dying during the interval *t*+26 cycles and *t*+50 cycles;
- ≥360 days from death – calculated as the complement of the sum of the probabilities of being in the other three states.

Table 17 summarises the EQ-5D-3L estimates applied using the company's time-to-death approach.

Table 17: Mean EQ-5D utilities used in the company's base case analyses (applied to all treatment groups)

Time-to-death category	Utility value
≥360 days	[redacted]
180 to 360 days	[redacted]
30 to 180 days	[redacted]
<30 days	[redacted]

Health utilities are adjusted by age through the application of utility decrements based on sex-specific UK general population utilities reported by Ara and Brazier.[98] These decrements are assumed to increase linearly until the age of 75 years; beyond this age, a constant decrement is applied each year. The CS[1] states that the HRQoL of caregivers was not included in the analyses due to a lack of data.

QALY losses associated with AEs

The model includes QALY losses associated with Grade 3-5 AEs for all treatment groups. The disutility for Grade 3-5 AEs was based on the difference between EQ-5D utility in patients who were progression-free with and without Grade 3-5 AEs in KEYNOTE-407,[7, 8] based on pooled data for both treatment groups. The methods for deriving these estimates (e.g. how time and multiple observations were dealt with) were not described in the CS.[1] This disutility was then multiplied by the mean duration of AEs observed in the trial ([redacted] days) and by the sum of the AE incidence rates within each trial arm (note – this value is normalised; this issue is discussed further in Section 5.3.3). Table 18 summarises the QALY losses applied to each treatment group in the model; each estimate is applied as a once-only health decrement during the first model cycle.

Table 18: Utilities, disutilities and QALY losses for Grade 3-5 AEs used in the model

Estimate	Pembrolizumab combination therapy (KEYNOTE-407[7, 8])	SC chemotherapy (KEYNOTE-407[7, 8])
Mean utility in patients with Grade 3-5 AEs	[redacted]	[redacted]
Mean utility in patients without Grade 3-5 AEs	[redacted]	[redacted]
Disutility of Grade 3-5 AEs	[redacted]	[redacted]
Mean QALY loss per patient due to Grade 3-5 AEs	[redacted]	[redacted]

AEs – adverse events

Treatment effects on PFS and OS from NMAs / indirect comparisons (applied in Base Case Analysis 2 and subgroup analyses)

A summary of the NMAs and ITC analysis undertaken by the company can be found in Section 4.4 of this report. The ERG notes that the NMAs used in the company's model were not presented in the CS[1] or the CS appendices.[11] The correct NMAs were later provided by the company as an additional analysis in response to a request for clarification from the ERG (see clarification response,[12] B9).

Resource costs

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) disease management; (iv) second-line therapy; (v) management of AEs and (vi) end-of-life (terminal care) costs. Table 19 summarises the costs for each treatment group in the company's base case analyses; the derivation of these values is described in the subsequent sections.

Table 19: Costs parameters for each comparator used in the model

Cost parameter	Pembrolizumab combination therapy*	Carboplatin+ paclitaxel/nab -paclitaxel	Platinum+ docetaxel	Platinum+ gemcitabine	Platinum+ paclitaxel
Drug costs* (per 3-week cycle)	[redacted]	£576.69	£48.90	£60.13	£53.06
RDI	93.50%	98.12%	98.12%	98.12%	98.12%
Administration costs (per 3-week cycle)	£607.52†	£433.52	£266.52	£471.29	£269.86
% of patients receiving 2nd line treatment	27.39%	51.92%	51.92%	51.92%	51.92%
2nd line treatment costs (once-only)	£571.87	£5,038.88	£5,038.88	£5,038.88	£5,038.88
Disease management – progression-free (weekly)	£89.53	£89.53	£89.53	£89.53	£89.53
Disease management – progressed disease (weekly)	£144.33	£144.33	£144.33	£144.33	£144.33
Terminal care (once-only)	£4,404.26	£4,404.26	£4,404.26	£4,404.26	£4,404.26
AEs	£1,256.99	£1,216.98	£1,216.98	£1,216.98	£1,216.98

AE – Adverse event; RDI: relative dose intensity;
** Includes CAA for pembrolizumab; † The ERG notes that the calculations used for the administration costs of pembrolizumab combination therapy are unusual – whilst this is likely to reflect an error, the magnitude of this is minor*

[redacted]*(i) Drug acquisition costs* [redacted]All first-line treatments are costed based on 3-weekly cycles. Treatment with pembrolizumab is assumed to have a maximum duration of 2 years (up to 35 administrations), whilst SC chemotherapy, either alone or in combination with pembrolizumab, is assumed to have a maximum duration of 4 treatment cycles (12 weeks). The acquisition costs for each cycle of pembrolizumab are calculated as a function of the cost per vial and a fixed dose per infusion. Based on its list price,[86] the cost per 100mg vial of pembrolizumab is £2,630; each treatment cycle requires 2

vials (pembrolizumab acquisition cost per treatment cycle = £5,260). The company currently has a CAA in place for pembrolizumab; the acquisition cost of pembrolizumab including the CAA is [redacted] per treatment cycle (discount from list price = [redacted]). The costs of paclitaxel, nab-paclitaxel and carboplatin were based on costs estimated from values from eMIT[85] and the use each regimen component within KEYNOTE-407.[7, 8] The acquisition costs for the SC chemotherapy regimens were based on market share data[99, 100] and prices from eMIT.[85] All drug acquisition drugs are adjusted by RDI estimates from the KEYNOTE-407 trial;[7, 8] the same RDI is assumed for all chemotherapies. Drug acquisition costs exclude wastage.

(ii) Drug administration costs

Administration costs for pembrolizumab and SC chemotherapy regimens were taken from the National Tariff Chemotherapy Regimens list 2017-2018[101] and NHS Reference Costs 2016/17[87] (see Table 20).

Table 20: Administration costs assumed for each treatment regimen

Regimen	Assumed administrations per cycle	Unit cost per administration	Source
Pembrolizumab	1 x SB12Z (outpatient)	£173.99	National Tariff Chemotherapy Regimen List 2017-2018[101] and NHS Reference Costs 2016/17[87]
nab-paclitaxel/carboplatin	1 x SB14Z (outpatient) + 2 x SB15Z (outpatient)	£680.04	
Docetaxel+carboplatin	1 x SB13Z (outpatient)	£264.56	
Docetaxel+cisplatin	1 x SB14Z (oupatient)	£269.86	
Gemcitabine+carboplatin	1 x SB13Z (outpatient) + 1 x SB15Z (outpatient)	£469.65	
Gemcitabine+cisplatin	1 x SB14Z (outpatient) + 1 x SB15Z (outpatient)	£474.95	
Paclitaxel+carboplatin	1 x SB14Z (outpatient)	£269.86	
Paclitaxel+cisplatin	1 x SB14Z (outpatient)	£269.86	

Source: CS[1] and company's model
SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance; SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance; SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance; SB15Z - Deliver subsequent elements of a chemotherapy cycle

The administration costs for each treatment regimen are also adjusted by the RDI observed in KEYNOTE-407.[7, 8]

(iii) Disease management costs

Health care resource use estimates include the costs associated with visits from GPs, nurses, therapists, outpatient appointments, examinations and tests and supportive care; different costs are estimated for patients who are progression-free and for those with progressed disease, although these states are not used in the model. The costs for PFS were derived from a variety of sources including: a previous health

technology assessment (HTA) report of first-line chemotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC (Brown *et al*[88]); the previous NICE appraisal of necitumumab for locally advanced or metastatic EGFR-expressing squamous NSCLC (TA411);[102] NHS Reference Costs 2016/17;[87] the Personal Social Services Research Unit (PSSRU),[103] and additional assumptions.[1] The mean costs associated with being progression-free or having progressed disease are assumed to be the same across all treatment options (see Table 19).

Management costs associated with being progression-free are applied to patients whilst they are receiving first-line treatment based on the TTD curves; for patients who go on to receive second-line treatment, these costs are applied indefinitely, irrespective of second-line treatment duration. Conversely, management costs associated with having progressed disease are applied only to those patients who have discontinued first-line treatment and do not go on to receive second-line treatment. The ERG does not consider this approach to be appropriate; this is discussed further in Section 5.3.3.

(iv) Second-line treatment costs

The model includes the costs of second-line treatment for a proportion of patients in all treatment groups based on IA2 of KEYNOTE-407;[7, 8] the second-line regimens available and the proportions of patients receiving these are assumed to differ by treatment group. Patients who discontinue first-line pembrolizumab treatment are assumed not to be eligible for second-line immunotherapy; instead, approximately 27.4% of patients are assumed to receive second-line treatment with SC chemotherapy (carboplatin/cisplatin in combination with gemcitabine, or docetaxel, gemcitabine or vinorelbine alone). Conversely, approximately 51.9% of patients in the SC chemotherapy comparator groups are assumed to be receive second-line treatment with immunotherapy (nivolumab or pembrolizumab [approximately [redacted] of patients]), chemotherapy (carboplatin/cisplatin in combination with gemcitabine, or docetaxel, gemcitabine or vinorelbine alone), or a combination of both. Clinical advisors to the ERG noted differences between the second-line treatments available in the trial and those available in usual clinical practice (e.g. patients who receive first-line platinum-doublet therapy would be unlikely to receive platinum-doublet therapy again, unless there was a prolonged period of remission). The costs associated with second-line drug acquisition and administration for each modelled treatment group are then generated by multiplying the distribution of the use of each drug observed in KEYNOTE-407[7, 8] by the relevant unit costs and the proportion of patients receiving each regimen (see Table 19). Second-line treatment costs are applied at the point of discontinuation of first-line therapy, rather than at the time of progression.

(v) AE management costs

Costs associated with managing AEs are calculated using the weighted average of the incidence of each Grade 3-5 AE in each treatment arm in KEYNOTE-407 and the unit cost for each AE type (see Table

21). Unit costs were taken from Brown *et al*,[88] previous NICE STA submissions,[74, 89-96] NHS Reference Costs,[87] clinical opinion and assumptions.[1] AEs costs were estimated to be [redacted] for the pembrolizumab combination therapy group and [redacted] for the SC chemotherapy group; these costs are applied once only during the first model cycle. AE costs for the SC chemotherapy NMA comparators are assumed to be the same as those for the carboplatin plus paclitaxel/nab-paclitaxel group.

Table 21: Incidence rates and unit costs for Grade 3-5 AEs used in the model

Adverse event	Pembrolizumab combination	Chemotherapy	Unit cost	Source
Nausea	[redacted]	[redacted]	£998.38	Brown *et al*[88]
Anaemia	[redacted]	[redacted]	£2,692.61	NICE TA428[89]
Fatigue	[redacted]	[redacted]	£2,855.25	Brown *et al*[88]
Decreased appetite	[redacted]	[redacted]	£0.00	NICE TA428[89]
Constipation	[redacted]	[redacted]	£0.00	Assumption
Diarrhoea (grade 2)	[redacted]	[redacted]	£456.66	NICE TA428[89]
Diarrhoea (grade 3-4)	[redacted]	[redacted]	£998.38	Brown *et al*[88]
Dyspnoea	[redacted]	[redacted]	£588.98	NICE TA403[90]
Vomiting	[redacted]	[redacted]	£813.47	NICE TA192[91]
Back pain	[redacted]	[redacted]	£0.00	Assumption
Arthralgia	[redacted]	[redacted]	£0.00	Assumption
Neutropenia	[redacted]	[redacted]	£120.99	Brown *et al*[88]
Oedema peripheral	[redacted]	[redacted]	£0.00	Assumption
Blood creatinine increased	[redacted]	[redacted]	£0.00	Assumption
Alanine aminotransferase increased	[redacted]	[redacted]	£637.03	NICE TA347[92]
Dizziness	[redacted]	[redacted]	£0.00	Assumption
Rash	[redacted]	[redacted]	£127.21	Brown *et al*[88]
Asthenia	[redacted]	[redacted]	£2,855.25	Brown *et al*[88]
Chest pain	[redacted]	[redacted]	£0.00	Assumption
Stomatitis	[redacted]	[redacted]	£0.00	NICE TA428[89]
Hyponatraemia	[redacted]	[redacted]	£0.00	NICE TA357[93]
Thrombocytopenia	[redacted]	[redacted]	£782.31	NICE TA406[94]
Neuropathy Peripheral	[redacted]	[redacted]	£0.00	Assumption
Abdominal pain	[redacted]	[redacted]	£0.00	NICE TA395[95]
Aspartate aminotransferase increased	[redacted]	[redacted]	£364.64	NICE TA347[92]
Peripheral Sensory Neuropathy	[redacted]	[redacted]	£0.00	Assumption
Pyrexia	[redacted]	[redacted]	£261.00	NHS Reference Costs 2016/17[87§]
Musculoskeletal pain	[redacted]	[redacted]	£0.00	Assumption
Pneumonia	[redacted]	[redacted]	£3,102.84	NICE TA411[74]
White blood cell count decreased	[redacted]	[redacted]	£577.66	NICE TA428[89]
Haemoptysis	[redacted]	[redacted]	£0.00	Assumption
Pain in extremity	[redacted]	[redacted]	£0.00	Assumption
Cough	[redacted]	[redacted]	£0.00	Assumption

Adverse event	Pembrolizumab combination	Chemotherapy	Unit cost	Source
Myalgia	[redacted]	[redacted]	£0.00	Assumption
Pruritis	[redacted]	[redacted]	£0.00	Assumption
Upper respiratory tract infection	[redacted]	[redacted]	£171.14	Assume the same as lower respiratory tract infection¤
Leukopenia	[redacted]	[redacted]	£0.00	NICE TA406[94]
Epistaxis	[redacted]	[redacted]	£0.00	Assumption
Neutrophil Count Decreased	[redacted]	[redacted]	£577.66	NICE TA428[89]
Pneumonitis	[redacted]	[redacted]	£3,102.84	Assumed to be same as pneumonia (TA395)[95]
Febrile neutropenia	[redacted]	[redacted]	£7,045.41	Brown *et al*[88]
Bronchitis	[redacted]	[redacted]	£171.14	Assume the same as lower respiratory tract infection¤
Platelet Count Decreased	[redacted]	[redacted]	£577.66	NICE TA428[89]
Weight decreased	[redacted]	[redacted]	£0.00	Assume same as decreased appetite (TA428)[89]
Hypothyroidism	[redacted]	[redacted]	£0.00	Assumption
Hypokalaemia	[redacted]	[redacted]	£465.00	NHS Reference Costs 16/17[87*]
Hypomagnesaemia	[redacted]	[redacted]	£465.00	NHS Reference Costs 16/17[87*]
Hyperthyroidism	[redacted]	[redacted]	£0.00	Assumed to be zero
Headache	[redacted]	[redacted]	£0.00	Assumed to be zero
Paraesthesia	[redacted]	[redacted]	£0.00	Assumed to be zero
Hypotension	[redacted]	[redacted]	£0.00	Assumed to be zero
Hypocalcemia	[redacted]	[redacted]	£465.00	NHS Reference Costs 2016/17[87*]

Source - CS[1] and company's model
Note - some costs have been inflated to 2016/17 using PSSRU inflation indices[103], § - WJ07B Fever of Unknown Origin with Interventions, with CC Score 0-3; - KC05G: Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+, ¤ - Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs (TA492)[96]*

(vi) End-of-life (terminal) costs

The model includes terminal care costs of £4,404 based on Brown *et al*;[88] these costs are applied at the point of death.

5.2.5 Subgroup analyses

The CS[1] presents the results of subgroup analyses based on the level of PD-L1 expression (TPS <1%, 1-49% and ≥50%). Within each PD-L1 subgroup, the model compares the cost-effectiveness of pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel, based on KEYNOTE-407.[7, 8] Within the PD-L1 TPS ≥50% subgroup, pembrolizumab combination therapy is compared against pembrolizumab monotherapy based on the company's indirect comparison of KEYNOTE-407 and KEYNOTE-042.[49]

The following sections detail modifications to the model parameters for Base Case Analysis 1 applied within the company's subgroup analyses.

Overall survival (subgroup analyses)

OS for pembrolizumab combination therapy and carboplatin plus paclitaxel/nab-paclitaxel is modelled as per Base Case Analysis 1, including the same SEER dataset and the same RR for death, but using subgroup-specific KM curves for each PD-L1 subgroup. OS for the pembrolizumab monotherapy group is modelled by raising the pembrolizumab combination therapy group OS to the power of the HR estimated from indirect comparison of KEYNOTE-407[7, 8] and KEYNOTE-042[49] (pembrolizumab monotherapy versus combination therapy HR=[redacted]). The ERG notes that this HR does not match the ITC results reported in the CS;[1] this error was corrected following the clarification stage - see Section 5.3.3). The OS curves used in the company's subgroup analyses are presented in Appendix 2.

Progression-free survival (subgroup analyses)

PFS is modelled using subgroup-specific KM curves and parametric (log normal) models for each PD-L1 subgroup. PFS for the pembrolizumab monotherapy group is modelled by raising the pembrolizumab combination therapy group PFS probabilities to the power of the HR estimated from indirect comparison of KEYNOTE-407[7, 8] and KEYNOTE-042[49] (pembrolizumab monotherapy versus combination therapy HR=[redacted]). The ERG notes that this ITC result does not match the ITC results reported in the CS;[1] however, as noted in Section 5.2.2, progression status does not impact on the ICER. The PFS curves used in the company's subgroup analyses are presented in Appendix 2.

Time to treatment discontinuation (subgroup analyses)

TTD is modelled using subgroup-specific KM curves for each PD-L1 subgroup. For the PD-L1 TPS≥50% subgroup, the model uses an exponential function for pembrolizumab combination therapy, rather than the generalised gamma function used in the company's base case analyses. The company's justification for selecting a different parametric curve for this subgroup was that the generalised gamma function predicted a cumulative TTD probability which "*descended to 0% treatment use by week 80, well prior to the 2-year maximum duration of treatment for pembrolizumab*"; the company notes that this was not seen for the overall population or for any other subgroups (CS Appendix N,[11] page 350). The exponential model was selected as this model had the lowest average AIC and BIC values (see Appendix 2, Table 46).

The ERG notes that according to the company's model, TTD for the pembrolizumab monotherapy group is modelled using the complete observed KM curve for *"Non-Squamous Patients With PD-1 ≥ 50% in KN024/KN042 Based on KM Curve"*; the ERG is unclear whether this is accurate as neither the

CS[1] nor the CS appendices[11] explain how TTD is modelled for the pembrolizumab monotherapy group. The TTD curves used in the company's subgroup analyses are presented in Appendix 2.

HRQoL (subgroup analyses)

Within the subgroup analyses, health utility is modelled as per the base case analyses for the pembrolizumab combination therapy and SC chemotherapy groups. For pembrolizumab monotherapy, ratios describing the utilities for pembrolizumab monotherapy compared with SC chemotherapy derived from EQ-5D data from KEYNOTE-024[17] were applied to the utilities for the SC chemotherapy arm in KEYNOTE-407.[7, 8] The CS does not explain why different utility values are used for this treatment group. A constraint is applied to the generated values for the pembrolizumab monotherapy group to ensure that the maximum utility value does not exceed [redacted]; this constraint impacts on the ≥360 days time-to-death category and is neither explained nor justified in the CS.

Table 22 summarises the EQ-5D estimates using the company's time-to-death approach for each treatment option evaluated in the PD-L1 subgroup analyses. Utilities are age-adjusted as per the base case analyses.

Table 22: Mean EQ-5D health utility scores used in the company's subgroup analyses

Time-to-death category	Pembrolizumab combination therapy (all subgroups)	SC chemotherapy (all subgroups)	Pembrolizumab monotherapy (PD-L1 TPS ≥50%)	
	Mean	Mean	Mean	Ratio (applied to SC chemotherapy group)
≥360 days	[redacted]	[redacted]	[redacted]	[redacted]
180 to 360 days	[redacted]	[redacted]	[redacted]	[redacted]
30 to 180 days	[redacted]	[redacted]	[redacted]	[redacted]
<30 days	[redacted]	[redacted]	[redacted]	[redacted]

PD-L1 - programmed death-ligand 1; SC - standard care

** This value is limited by an unexplained constraint applied in the company's model*

AE QALY losses (subgroup analyses)

QALY losses associated with AEs for pembrolizumab combination therapy and SC chemotherapy are the same as those applied in the company's base case analyses. Within the pembrolizumab monotherapy group (PD-L1 TPS ≥50% subgroup), the disutility associated with Grade 3-5 AEs was estimated as the difference between the mean utility for progression-free patients with and without Grade 3-5 AEs in the pembrolizumab arm of KEYNOTE-024.[17] This disutility was multiplied by the mean duration of AEs in KEYNOTE-407 trial[7, 8] and by the sum of the AE incidence rates within the pembrolizumab monotherapy arm of KEYNOTE-024.[17] The estimated QALY loss is summarised in Table 23.

Table 23: Utilities, disutilities and QALY losses for Grade 3-5 AEs in the company's subgroup analyses

	Pembrolizumab combination (all subgroups)*	SC chemotherapy (all subgroups)*	Pembrolizumab monotherapy (PD-L1≥50%)†
Mean utility in patients with Grade 3-5 AEs	[redacted]	[redacted]	[redacted]
Mean utility in patients without Grade 3-5 AEs	[redacted]	[redacted]	[redacted]
Disutility of Grade 3-5 AEs	[redacted]	[redacted]	[redacted]
Mean QALY loss per patient due to Grade 3-5 AEs	[redacted]	[redacted]	[redacted]

AEs - adverse events; PD-L1 - programmed death-ligand 1; QALY - quality-adjusted life year
** - KEYNOTE-407;[7] † - KEYNOTE-024.[17]*

Resource costs (subgroup analyses)

Costs associated with acquisition and administration of pembrolizumab monotherapy are estimated using a similar approach to the options included in the base case analyses. RDI and TTD were based on data from the KEYNOTE-024 trial.[17] The costs applied in the subgroup analyses are shown in Table 24.

Table 24: Costs parameters for each comparator used in the company's subgroup analyses

Cost parameter	Pembrolizumab combination*	Standard chemotherapy	Pembrolizumab monotherapy* (TPS≥50%)
Drug costs* (per 3-week cycle)	[redacted]	£576.69	[redacted]
RDI	93.50%	98.12%	99.00%
Administration costs (per 3-week cycle)	£607.52	£433.52	£173.99
% of patients receiving 2nd line treatment	27.4%	51.9%	31.0%
2nd line treatment costs (once-only)	£571.87	£5,038.88	£547.16
Disease management - progression-free (weekly)	£89.53	£89.53	£89.53
Disease management - progressed disease (weekly)	£144.33	£144.33	£144.33
Terminal care (once-only)	£4,404.26	£4,404.26	£4,404.26
AEs	£1,256.99	£1,216.98	£1,107.69

AE: adverse event; PFS: progression-free state; PD-L1: programmed death-ligand 1; PD: progressive disease state; RDI: relative dose intensity;
** Includes CAA for pembrolizumab*

The probability of receiving second-line treatment and associated costs for pembrolizumab monotherapy were based on data from KEYNOTE-024.[17] In line with the company's base case analyses, the model assumes that patients who discontinue first-line pembrolizumab monotherapy are not eligible for second-line immunotherapy; for these patients, second-line treatment is assumed to be comprised of SC chemotherapy including a platinum drug (carboplatin+gemcitabine or carboplatin/cisplatin+paclitaxel). The model applies different second-line treatment regimens from

KEYNOTE-024[17] for this option only. Second-line treatment costs for patients receiving SC chemotherapy or pembrolizumab combination therapy are assumed to be the same as those applied in the base case analyses; these costs are applied at the point of discontinuation for first-line treatment.

Disease management costs and terminal costs are the same as those applied in the base case analyses.

Costs associated with Grade 3-5 AEs for pembrolizumab monotherapy are based on incidence rates from KEYNOTE-024[17] (see Appendix 2); these used the same unit costs as those applied in the company's base case analyses. The model estimates a mean cost of [redacted] for managing AEs in the pembrolizumab monotherapy group. AE costs for pembrolizumab combination therapy and for SC chemotherapy are assumed to be the same as those applied in the company's base case analyses.

5.2.6 Model evaluation methods

The CS[1] presents the results of the base case analyses in terms of the incremental cost per QALY gained for pembrolizumab combination therapy versus SC chemotherapy using pairwise comparisons. The company's base case ICERs were generated using the deterministic version of the model. The CS also includes the results of probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSAs), and scenario analyses for Base Case Analysis 1 (the comparison against carboplatin plus paclitaxel/nab-paclitaxel); these analyses were not undertaken for Base Case Analysis 2 (comparisons against SC regimens in the NMA). Subgroup analyses are also presented according to PD-L1 TPS.

The results of the PSA are presented in the form of a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs), based on 1,000 Monte Carlo simulations. The probabilistic ICER, based on the expectation of the mean, is also presented within the CS.[1] The distributions applied in the company's PSA are summarised in Table 25. The results of the DSAs were presented in the form of a tornado diagram for specified model parameters. Scenario analyses were undertaken to explore the impact of: using alternative cut-points and parametric distributions for OS and PFS; using alternative BSA calculations; removing the half-cycle correction; applying alternative assumptions regarding the proportionate use of paclitaxel/nab-paclitaxel; using alternative assumptions regarding HRQoL, and applying an assumption regarding the loss of OS treatment effect for pembrolizumab combination therapy.

Table 25: Distributions used in company's PSA, base case and subgroup analyses

Parameter / parameter group	Distribution	ERG comment
Patient characteristics (age, BSA, weight)	Fixed	-
PFS - carboplatin+paclitaxel/ nab-paclitaxel	MVN (parametric portion only)	No uncertainty included prior to 26-week cut-point. PFS does not affect ICER.
PFS - pembrolizumab combination therapy	MVN (parametric portion only)	No uncertainty included prior to 26-week cut-point. PFS does not affect ICER.
OS - carboplatin+paclitaxel/ nab-paclitaxel	Fixed / log normal	No uncertainty included for the first 52 weeks. Arbitrary log normal distribution applied to SEER baseline OS data.
OS - pembrolizumab combination therapy	Fixed / log normal	
Mortality - general population	Fixed	-
TTD - pembrolizumab combination therapy	MVN	-
TTD - carboplatin+paclitaxel/ nab-paclitaxel	Normal	Sampled "% variation" parameter is linked to a blank cell, hence no uncertainty is modelled
TTD - pembrolizumab monotherapy (PD-L1 TPS ≥50% subgroup analysis only)	MVN	Uncertainty surrounding observed data from KEYNOTE-042/024 modelled using arbitrary normal distribution
HRQoL applied in health states	Beta	Utility parameters sampled independently for each treatment group; for any given sample, patients in the same health state will have a different level of HRQoL depending on which treatment they receive.
QALY loss resulting from AEs	Probability – beta Disutility – beta Duration – normal	-
HRs for PFS (NMA comparators versus pembrolizumab combination therapy)	Log normal	Sampled from log normal distribution for pairwise comparison. Use of CODA samples would capture correlation in treatment effects across the entire network.
HRs for OS (NMA comparators versus pembrolizumab combination therapy)	Log normal	
HR for PFS (pembrolizumab monotherapy versus pembrolizumab combination therapy, PD-L1 TPS ≥50% subgroup only)	Log normal	
HR for OS (pembrolizumab monotherapy versus pembrolizumab combination, PD-L1 TPS ≥50% only)	Log normal	-
Drug acquisition costs	Fixed	-
Drug administration costs	Log normal	Given that this cost was derived from a large sample, a normal distribution with SE derived from the IQR may be more appropriate.
RDI	Log normal	Truncated to maximum value of 1.0. A beta distribution may been more appropriate.
Disease management costs	Log normal	SE arbitrarily assumed to be equal to 10% of mean.
Second-line therapy costs	Log normal	SE arbitrarily assumed to be equal to 10% of mean.
Costs associated with AEs	Log normal	–

AE - adverse event; BSA - body surface area; CODA - convergence diagnostic and output analysis; HRQoL - health-related quality of life; IQR - interquartile range; OS - overall survival; PD-L1 - programmed death-ligand 1; PFS - progression-free survival; QALY - quality-adjusted life years; SE - standard error; TPS - tumour proportion score; MVN - multivariate normal

5.2.7 Company's model validation and verification

The CS[1] states that the OS predictions from the model were compared against those observed within KEYNOTE-407;[7, 8] the outcomes of this comparison are presented in Table 26. With respect to this validation exercise, the ERG notes the following:

- The data presented in Table 26 suggest a considerable difference between the observed and predicted values. This is partly because the reported estimate of 48.3 months is incorrect; the correct estimate of the median model-predicted OS for pembrolizumab combination therapy is approximately 20.5 months. Comparing the observed and the correct predicted median OS still suggests that the company's model over-estimates survival for the pembrolizumab combination therapy group (observed median OS in KEYNOTE-407 = 15.9 months).
- The model-predicted OS for the SC chemotherapy group reported in CS Appendix J is also incorrect. The correct value for the SC chemotherapy group is approximately 11.5 months; this is similar to the observed median survival of 11.3 months in KEYNOTE-407.
- The company's OS validation exercise suggests a very close match between the observed and predicted OS in both treatment groups at 1-year. However, this is because the model uses the observed OS data until the 1-year timepoint.
- There are no observed data at any selected timepoint beyond 1 year, hence this exercise provides no information to either support or refute the validity of the company's model predictions.

These issues are further discussed in Section 5.3.3.

Table 26: Comparison of observed and predicted OS – Base Case Analysis 1, pembrolizumab combination therapy versus cisplatin plus paclitaxel/nab-paclitaxel in KEYNOTE-407[7, 8] (adapted from CS Appendix J, Table J1). ERG-corrected values are presented in parentheses

Outcome	Pembrolizumab combination		Chemotherapy	
	Base case	KEYNOTE-407[7, 8]	Base case	KEYNOTE-407[7, 8]
Median OS (months)	48.3 (20.5)	15.9	21.15 (11.5)	11.3
1-year OS	65.1%	65%	48.2%	48%
2-year OS	45.0%	-	22.0%	-
5-year OS	26.0%	-	8.0%	-
10-year OS	16.3%	-	3.4%	-
20-year OS	8.7%		1.1%	

OS – overall survival

The CS states that the OS predictions for the base case analyses were validated with clinical experts; however, no results were presented for this validation.

The CS also states that the model approach and inputs were validated by two external health economists (Professor Chris Bojke, from the University of Leeds and Professor Alistair Gray from the University of Oxford). According to the CS, the model structure, selection of appropriate datasets, survival analysis, assumptions and utility values were all discussed with the experts.

5.2.8 Company's cost-effectiveness results (including existing CAA)

This section summarises the results presented in the CS.[1] It should be noted that the model contains several errors; the model results incorporating the corrections of these errors are presented as part of the ERG's exploratory analyses in Section 5.4.

Central estimates of cost-effectiveness (Base Case Analysis 1)

Table 27 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (Base Case Analysis 1). The probabilistic version of the model suggests that pembrolizumab combination therapy is expected to generate an additional 1.68 QALYs at an additional cost of £48,387 per patient; the corresponding ICER is £28,852 per QALY gained. The deterministic version of the model produces a slightly lower ICER of £28,672 per QALY gained.

Table 27: Company's results - Base Case Analysis 1, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs*	QALYs	Cost	ICER (per QALY gained)
Probabilistic model							
Pembrolizumab combination	NR†	2.95	£72,745	NR†	1.68	£48,387	**£28,852**
Carboplatin+paclitaxel/ nab-paclitaxel	NR†	1.27	£24,358	-	-	-	-
Deterministic model							
Pembrolizumab combination	5.09	2.95	£72,695	3.12	1.68	£48,278	**£28,672**
Carboplatin+paclitaxel/ nab-paclitaxel	1.97	1.27	£24,417	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*
† LYGs not recorded in company's PSA sub-routine

Central estimates of cost-effectiveness (Base Case Analysis 1 and 2)

The CS[1] presents pairwise ICERs for pembrolizumab combination therapy versus each of the SC chemotherapy comparators from the company's NMA, but excludes the KEYNOTE-407 trial comparator. The ERG considers it more appropriate to include all options within a fully incremental

analysis. Table 28 presents the results of a fully incremental analysis of all options included in both Base Case Analyses 1 and 2. This analysis suggests that: cisplatin/carboplatin plus docetaxel is the least effective option; carboplatin plus paclitaxel/nab-paclitaxel (the KEYNOTE-407 comparator) is dominated by cisplatin/carboplatin plus paclitaxel; the ICERs for cisplatin/carboplatin plus gemcitabine and cisplatin/carboplatin plus paclitaxel versus their next best non-dominated comparators are less than £9,000 per QALY gained, and the ICER for pembrolizumab combination therapy versus cisplatin/carboplatin plus gemcitabine is approximately £63,661 per QALY gained. It should be noted that the ERG has identified errors in the model which render these results unreliable (see Section 5.3.3).

Table 28: Company's results - Base Case Analysis 1 and 2, fully incremental analysis of pembrolizumab combination therapy and all comparators, deterministic model

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs*	QALYs	Cost	ICER (per QALY gained)
Pembrolizumab combination	5.09	2.95	£72,695	1.00	0.66	£41,748	**£63,661**
Platinum+gemcitabine	4.09	2.30	£30,947	2.11	1.03	£8,945	**£8,725**
Platinum+paclitaxel	1.97	1.27	£22,002	0.19	0.10	£818	**£8,203**
Carboplatin+paclitaxel/ nab-paclitaxel	1.97	1.27	£24,417	-	-	-	**Dominated**
Platinum +docetaxel	1.78	1.17	£21,184		-	-	-

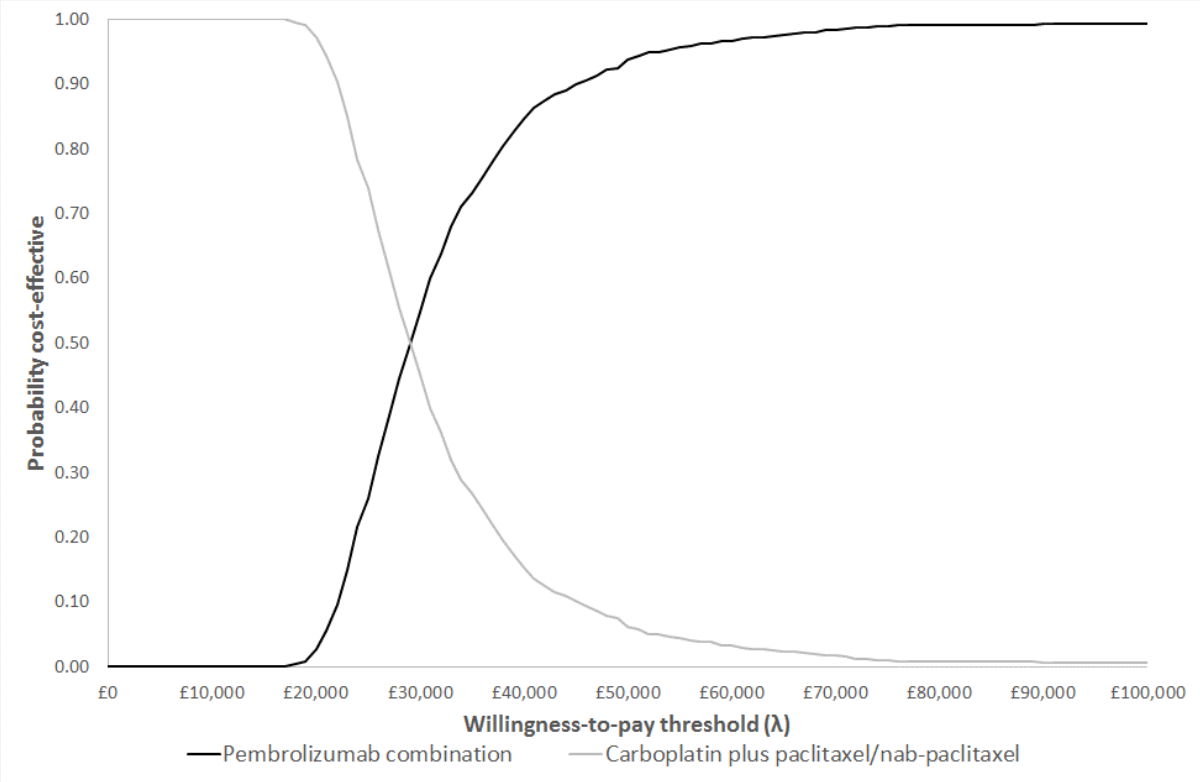
LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** undiscounted*

Company's probabilistic sensitivity analysis (Base Case Analysis 1)

Figure 14 presents the CEACs for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (Base Case Analysis 1). The probability that pembrolizumab combination therapy produces more net benefit than carboplatin plus paclitaxel/nab-paclitaxel at willingness-to-pay (WTP) thresholds of £30,000 and £50,000 per QALY gained is 0.55 and 0.94, respectively.

The CS[1] does not include CEACs for comparisons of pembrolizumab combination versus the SC chemotherapy comparator regimens from the NMA (Base Case Analysis 2).

Figure 14: Company's results – Base Case Analysis 1, CEACs, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (generated by the ERG)

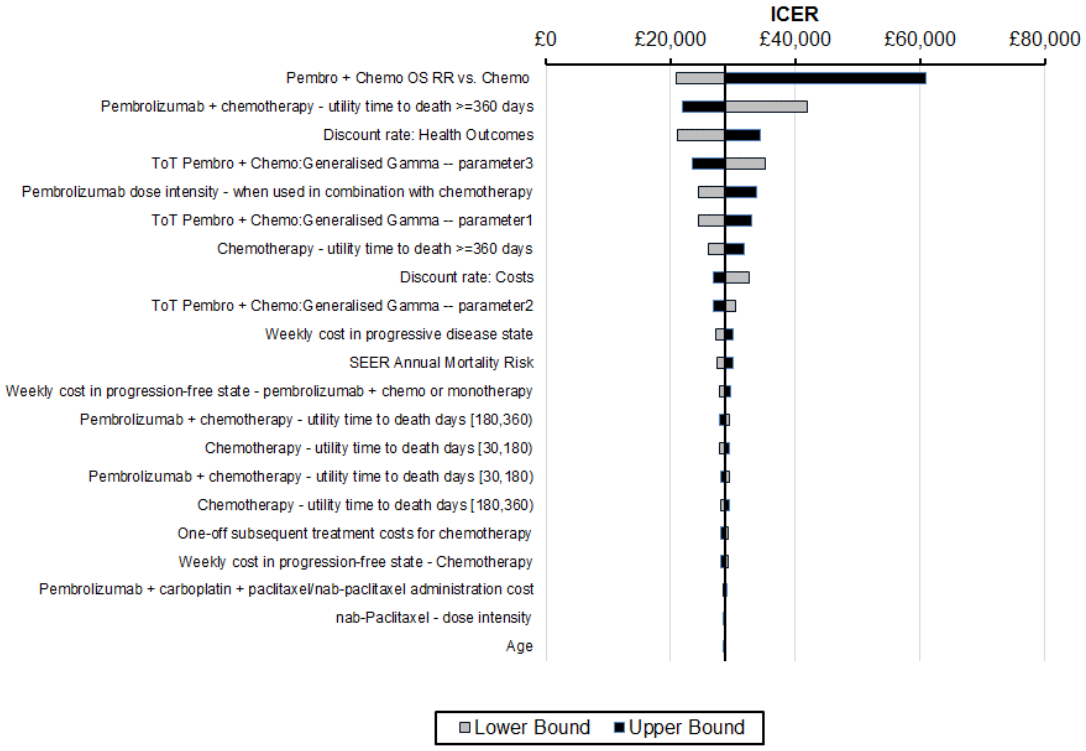


Company's deterministic sensitivity analyses (Base Case Analysis 1)

Figure 15 presents the results of the company's DSAs in the form of a tornado diagram for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (Base Case Analysis 1). Based on these analyses, the ICER is estimated to range from £20,842 to £60,849 per QALY gained. These analyses suggest that the most influential model parameters are the RR of death applied in the pembrolizumab combination therapy group for all model cycles after month 12, the utility value applied for patients who are ≥360 days from death and the discount rate for health outcomes.

The CS[1] does not include tornado plots for comparisons of pembrolizumab combination versus the SC chemotherapy comparator regimens from the NMA (Base Case Analysis 2).

Figure 15: Company's results - Base Case Analysis 1, deterministic sensitivity analyses, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (adapted from the company's model)



Company's scenario analyses (Base Case Analysis 1)

Table 27 summarises the results of the company's scenario analyses for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel. The analyses suggest that the ICER is particularly sensitive to assumptions regarding the OS model assumed for the pembrolizumab combination therapy group. In addition, the inclusion of a loss of treatment effect at 5 years leads to a moderate increase in the ICER. The table also shows that the PFS parameters have no impact on the model results, except in the scenario in which utilities are defined by the presence/absence of disease progression (company's scenario analysis 6).

The CS[1] does not present scenario analyses for comparisons of pembrolizumab combination therapy versus the SC chemotherapy comparator regimens from the NMA (Base Case Analysis 2).

Table 29: Company's results - Base Case Analysis 1, scenario analyses, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (adapted from CS Table 91)

Scenario reference	Scenario description	Incremental - pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel		
		QALYs	Costs	ICER
-	Company's Base Case Analysis 1	1.68	£48,278	**£28,672**
Scenario 1a	OS modelled using KM and exponential model (19 weeks cut-off)	0.46	£36,989	**£80,142**
Scenario 1b	OS modelled using KM and log logistic model (19 weeks cut-off)	0.84	£41,053	**£48,706**
Scenario 2a	PFS modelled using log normal (16 weeks cut-off)	1.68	£48,278	**£28,672**
Scenario 2b	PFS modelled using log normal (36 weeks cut-off)	1.68	£48,278	**£28,672**
Scenario 3	UK-specific BSA values (unadjusted by sex distribution)*	1.68	£48,279	**£28,673**
Scenario 4	No half cycle correction	1.68	£48,222	**£28,649**
Scenario 5	100% paclitaxel use (0% nab-paclitaxel use)	1.68	£48,326	**£28,700**
Scenario 6	Utilities defined by progression status (pooled)	1.49	£48,278	**£32,320**
Scenario 7a	Utilities defined by time to death (per treatment arm)	1.58	£48,278	**£30,580**
Scenario 7b	Utilities defined by progression status (per treatment arm)	1.53	£48,278	**£31,567**
Scenario 8	No age-related disutilities	1.81	£48,278	**£26,737**
Scenario 9	Treatment effect removed at beginning of year 5	1.15	£43,444	**£37,730**
Scenario 10	PFS modelled using generalised gamma model (26 weeks cut-off)	1.68	£48,278	**£28,672**

ICER - incremental cost-effectiveness ratio; OS - overall survival; PFS - progression-free survival; QALY - quality-adjusted life year
** The ERG was unable to replicate this scenario analysis using the company's model*

Company's subgroup analyses

Table 30 presents the results of the company's subgroup analyses by PD-L1 TPS category. The company's subgroup analyses suggest the following:

- Within the PD-L1 TPS <1% subgroup, the company's model suggests that the ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel is £26,012 per QALY gained.
- Within the PD-L1 TPS 1-49% subgroup, the company's model suggests that the ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel is £32,174 per QALY gained.
- Within the PD-L1 TPS ≥50% subgroup, a fully incremental analysis of the available options suggests that pembrolizumab combination therapy is ruled out due to extended dominance (by

pembrolizumab monotherapy and carboplatin+paclitaxel/nab-paclitaxel). As the company's original submitted model uses an incorrect HR for this analysis, the ERG believes that the results for this subgroup are invalid and should be disregarded (corrected results are presented in Section 5.3.3, Table 34).

Table 30: Results of the company's subgroup analyses by PD-L1 TPS category

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs*	QALYs	Cost	ICER (per QALY gained)
PD-L1 TPS<1%							
Pembrolizumab combination	5.00	2.90	£70,000	3.15	1.71	£44,557	**£26,012**
Carboplatin+paclitaxel/ nab-paclitaxel	1.85	1.19	£25,443		-	-	-
PD-L1 TPS 1-49%							
Pembrolizumab combination	5.13	2.98	£78,721	3.11	1.68	£54,013	**£32,174**
Carboplatin+paclitaxel/ nab-paclitaxel	2.02	1.30	£24,708		-	-	-
PD-L1 TPS ≥50%							
Pembrolizumab monotherapy	5.86	3.32	£76,963	3.86	2.03	£52,562	**£25,849**
Pembrolizumab combination	4.93	2.86	£69,030	-	-	-	**extendedly dominated**
Carboplatin+paclitaxel/ nab-paclitaxel	2.00	1.29	£24,401	-	-	-	-

** undiscounted*
ICER - incremental cost-effectiveness ratio; LYG - life year gained; PD-L1: programmed death-ligand 1; QALY - quality-adjusted life year; TPS - tumour proportion score

5.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[104, 105]
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Examination of the correspondence between the description of the model reported in the CS[1] and the company's executable model.

- Replication of the base case results, PSA, DSAs and scenario analyses presented within the CS.[1]
- Where possible, checking of parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

5.3.1 Model verification

The ERG rebuilt the deterministic version of the company's base case model in order to verify its implementation. As shown in Table 31, the ERG's results are almost identical to those generated using the company's original submitted model. During the process of rebuilding the model, the ERG identified several programming errors which impact upon the model results. These errors, together with broader conceptual issues around the model structure and use of evidence to inform model parameters, are discussed in Section 5.3.3.

Table 31: Comparison of company's base case results and ERG's rebuilt model results (excluding corrections of errors)

Model outcome	Company's model			ERG's rebuilt model		
	Pembrolizumab combination	Comparator	Inc.	Pembrolizumab combination	Comparator	Inc.
Base Case Analysis 1 - overall population, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel						
LYGs	4.03	1.76	2.26	4.03	1.76	2.26
QALYs	2.95	1.27	1.68	2.95	1.27	1.68
Costs	£72,695	£24,417	£48,278	£72,695	£24,417	£48,278
ICER	-	-	**£28,672**	-	-	**£28,672**
Base Case Analysis 2 - overall population, pembrolizumab combination therapy versus cisplatin/ carboplatin plus docetaxel (NMA comparator)						
LYGs	4.03	1.63	2.39	4.03	1.63	2.39
QALYs	2.95	1.17	1.78	2.95	1.17	1.78
Costs	£72,695	£21,184	£51,511	£72,695	£21,184	£51,511
ICER	-	-	**£28,927**	-	-	**£28,927**
Base Case Analysis 2 - overall population, pembrolizumab combination therapy versus cisplatin/ carboplatin plus gemcitabine (NMA comparator)						
LYGs	4.03	3.16	0.86	4.03	3.16	0.86
QALYs	2.95	2.30	0.66	2.95	2.30	0.66
Costs	£72,695	£30,947	£41,748	£72,695	£30,947	£41,748
ICER	-	-	**£63,661**	-	-	**£63,661**
Base Case Analysis 2 - overall population, pembrolizumab combination therapy versus cisplatin/ carboplatin plus paclitaxel (NMA comparator)						
LYGs	4.03	1.77	2.26	4.03	1.77	2.26
QALYs	2.95	1.27	1.68	2.95	1.27	1.68
Costs	£72,695	£22,002	£50,693	£72,695	£22,002	£50,693
ICER	-	-	**£30,156**	-	-	**£30,157**

Subgroup Analysis - PD-L1 TPS <1%, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel						
LYGs	3.96	1.66	2.30	3.96	1.66	2.30
QALYs	2.90	1.19	1.71	2.90	1.19	1.71
Costs	£70,000	£25,443	£44,557	£70,000	£25,443	£44,557
ICER	-	-	**£26,012**	-	-	**£26,012**
Subgroup Analysis - PD-L1 TPS 1-49%, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel						
LYGs	4.06	1.80	2.26	4.06	1.80	2.26
QALYs	2.98	1.30	1.68	2.98	1.30	1.68
Costs	£78,721	£24,708	£54,013	£78,721	£24,708	£54,013
ICER	-	-	**£32,174**	-	-	**£32,174**
Subgroup Analysis - PD-L1 TPS ≥50%, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel						
LYGs	3.90	1.79	2.11	3.90	1.79	2.12
QALYs	2.86	1.29	1.57	2.86	1.29	1.57
Costs	£69,030	£24,401	£44,628	£69,030	£24,401	£44,628
ICER	-	-	**£28,380**	-	-	**£28,380**
Subgroup Analysis - PD-L1 TPS ≥50%, pembrolizumab combination therapy versus pembrolizumab monotherapy						
LYGs	3.90	4.55	-0.65	3.90	4.55	-0.65
QALYs	2.86	3.32	-0.46	2.86	3.32	-0.46
Costs	£69,030	£76,963	-£7,933	£69,030	£76,963	-£7,934
ICER	-	-	**£17,213**	-	-	**£17,213**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; PD-L1 - programmed death-ligand 1; QALY - quality-adjusted life year; TPS - tumour proportion score

5.3.2 Adherence to the NICE Reference Case

The company's economic analysis of pembrolizumab combination therapy for untreated metastatic squamous NSCLC is generally in line with the NICE Reference Case.[106]

Table 32: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's health economic analysis is generally in line with the final NICE scope.[6] As noted in Section 5.2.1, pembrolizumab has not yet been granted an EU marketing authorisation in this indication.
Comparator(s)	As listed in the scope developed by NICE	The NICE scope[6] specifies two comparators: (1) Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with carboplatin or cisplatin; (2) Pembrolizumab monotherapy (for people with tumours that express PD-L1 with at least 50% TPS with no EGFR- or ALK-positive tumour mutations only). The company's analysis does not include vinorelbine-including regimens as these were not used in KEYNOTE-407[7, 8] or in the studies identified for inclusion in the company's NMAs for the squamous PD-L1 unselected population.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are valued in terms of QALYs gained.
Perspective on costs	NHS and PSS	The analysis adopts an NHS and PSS perspective. The CS[1] (Table 56) states that "*PSS costs have not been considered due to the unavailability of data to incorporate this into the model."* However, scrutiny of the model indicates that some relevant PSS costs have been included in the company's model (e.g. community nurse visits).
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The results of the analyses are presented in terms of the incremental cost per QALY gained for pembrolizumab combination therapy versus SC chemotherapy (and pembrolizumab monotherapy in the PD-L1 TPS ≥50% subgroup).
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 30-year time horizon. At this point, the model suggests that 99.74% of patients receiving SC chemotherapy will have died. However, over 2% of the pembrolizumab combination therapy are predicted to still be alive at 30 years. Issues relating to the extrapolation of time-to-event outcomes are discussed in Section 5.3.3.
Synthesis of evidence on health effects	Based on systematic review	The company's NMA includes trials identified through a systematic review.

Element	Reference case	ERG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Whilst there is ambiguity in the CS, the company's clarification response[12] states that HRQoL estimates used in the model were based on EQ-5D-3L data collected within the KEYNOTE-407 trial. Preference-based utilities were valued using the UK tariff. The subgroup analysis in patients with PD-L1 TPS≥50% includes relative utility multipliers for the pembrolizumab monotherapy group. No justification of this approach is given in the CS or the CS appendices. Table 56 of the CS states that health impacts on caregivers were not included in the analysis *"due to the unavailability of data to incorporate this into the model."*
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains. The CS argues that pembrolizumab combination therapy meets NICE's End of Life criteria within the untreated squamous NSCLC population. This is discussed further in Chapter 6.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource costs include those relevant to the NHS and PSS. Unit costs were valued at 2016/17 prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum.

Main issues identified within the critical appraisal

Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's economic analyses. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified within the critical appraisal undertaken by the ERG

(1)	Identification of model errors
(2)	Unclear interpretation of effectiveness of SC chemotherapy comparators
(3)	Issues surrounding company's NMAs and ITCs
(4)	Uncertainty surrounding long-term extrapolation
(5)	Assumption of lifetime relative risk for OS for pembrolizumab combination therapy versus SC chemotherapy
(6)	Inclusion of an implicit assumption of cure
(7)	Concerns regarding the company's approach to modelling HRQoL
(8)	Uncertainty surrounding use second-line immunotherapy in the SC chemotherapy groups
(9)	Clinically unrealistic assumptions regarding disease management costs
(10)	Issues relating to AEs

(1) Identification of model errors

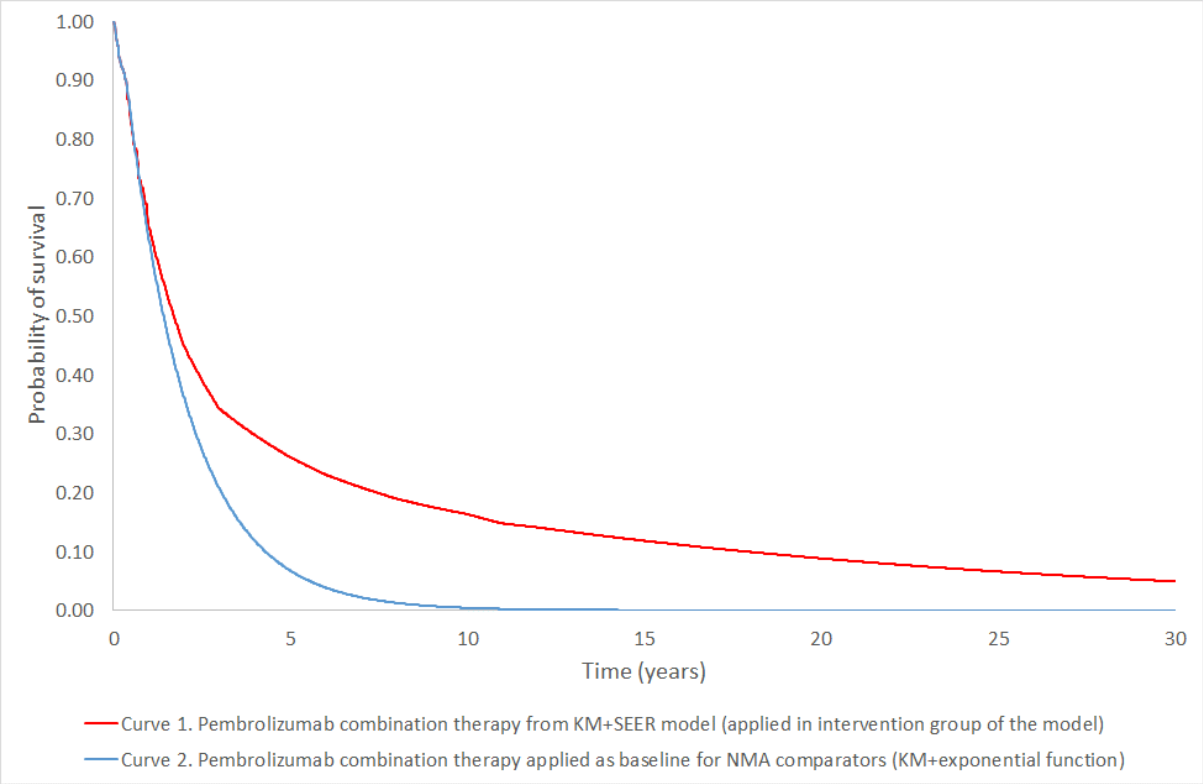
(i) Errors in the company's estimates of OS for all SC chemotherapy comparators included in the NMA (Base Case Analysis 2)

Whilst not clearly described in the CS,[1] it appears that the model intends to apply the HRs for OS from NMA3 (squamous, PD-L1 unselected, platinum drugs combined) using the pembrolizumab combination group OS function as a baseline. The ERG believes this to be the case because: (a) this is how PFS is modelled for the comparators from the NMA; (b) this is the approach used to model OS for pembrolizumab monotherapy in the PD-L1 TPS ≥50% subgroup; (c) within the model, prior to adjusting for general population mortality, OS in the pembrolizumab combination therapy group is raised to the power of the HR, and (d) all of the input parameters relating to HRs for OS in the model are greater than 1.0 (i.e. the comparator is less effective than the intervention). However, the ERG believes that the OS functions for the NMA comparators are subject to two mathematical errors which render the ICERs for Base Case Analysis 2 unreliable. The presence of these errors can be illustrated by setting the HRs from the NMA equal to 1.0 (removing the treatment effect of pembrolizumab combination therapy) – when this change is applied, the model erroneously suggests that the NMA comparators produce 1.13 LYGs more than pembrolizumab combination therapy – if all treatment options have equal efficacy, the incremental survival gain under this scenario should be zero. The reasons underpinning these errors are described below.

HRs for OS for NMA comparators applied to incorrect baseline OS function

The first error relates to the baseline upon which the treatment effect of the comparator is applied for OS. This is contained in column AK of worksheet 'NMA-ITC OS (conHR)' of the company's model. These baseline OS probabilities are raised to the power of the HRs for OS (NMA comparators versus pembrolizumab combination therapy) in column AL:AN of the same worksheet. These HR-adjusted survivor functions are applied in the model (in worksheet 'Modeled OS' columns AG:AI). However, the baseline survivor function in column AK relates is the KM/exponential model, not the KM/SEER model. This issue is illustrated in Figure 16: given the ERG's understanding of the company's intended approach, the analysis should use Curve 1 as the baseline function, but instead Curve 2 is used.

Figure 16: Illustration of incorrect baseline survivor function applied in company's analysis of NMA comparators

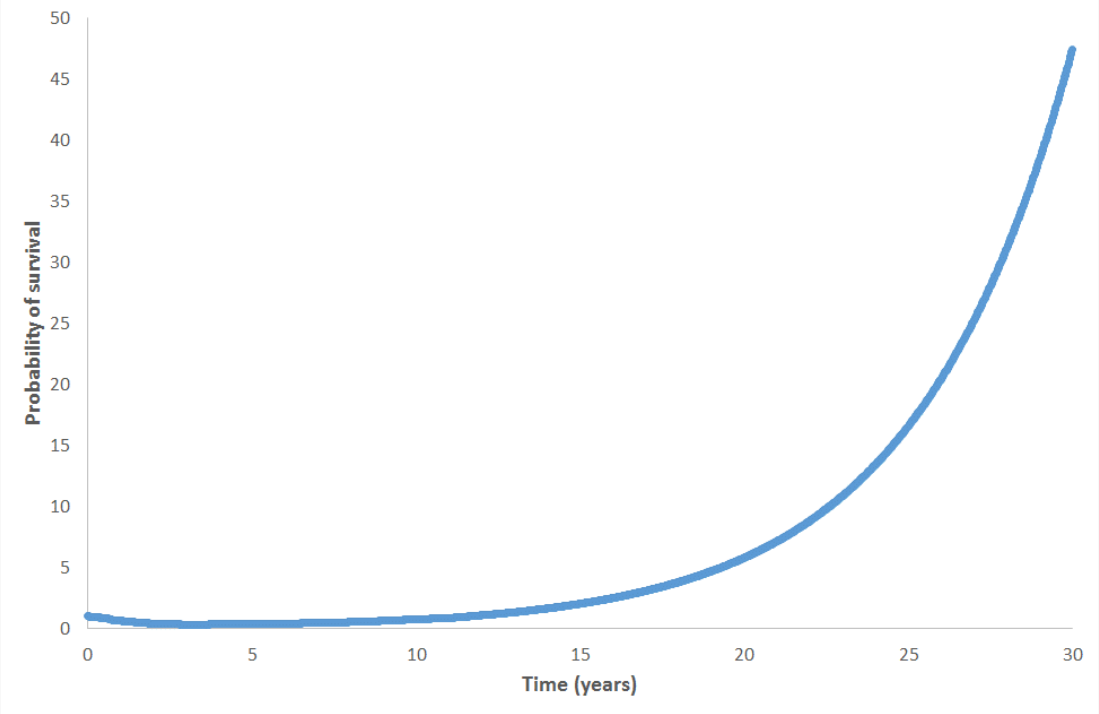


In response to a request for clarification on this issue from the ERG (clarification response,[12] question B31), the company stated *"The data in column AK, and on the worksheet generally, only reflect implementation of the parametric extrapolation approach for the indirect comparators. The SEER-based approach is implemented for the indirect treatment comparators on the 'Modeled OS' worksheet in the formulae in columns Y to AA. Therefore there is not an error."* The ERG believes that the company's response is incorrect: the formulae in column AK are fed through the model and these directly impact on the ICERs of pembrolizumab combination therapy versus all of the NMA comparators.

Incorrect formulae applied in OS model calculations for NMA comparators

The second error in Base Case Analysis 2 relates to the implementation of the OS model (given the wrong baseline OS function described above). In worksheet 'Modeled OS', the model draws in unadjusted OS functions and compares the mortality risk for each treatment group against the mortality risks in the general population, based on interim life tables. The higher of the two risks is then applied in each model cycle. For the NMA SC chemotherapy comparators, these formulae multiply the cumulative probability of surviving up to time *t* in the NMA comparator group by the conditional probability of surviving during the interval between *t* and *t*-1 in the modelled carboplatin plus paclitaxel/nab-paclitaxel group (KM/exponential model) divided by the conditional probability of surviving during the interval *t* and *t*-1 in the modelled carboplatin plus paclitaxel/nab-paclitaxel group (KM/SEER model). The ERG is unclear what this calculation is attempting to do, why any part of the calculation should relate to the KEYNOTE-407 trial comparator group, and why different OS models are being used for the SC chemotherapy group in the same calculation (KM/SEER and KM/exponential). What is clear however, is that when the HRs for OS for the NMA comparators are set equal to 1.0 (i.e. the treatment effects are removed) and the general population mortality risk is set equal to zero (the mortality constraint is removed), the predicted OS probability for the NMA chemotherapy comparators initially drops but then increases to values which are considerably greater than 1.0 (see Figure 17). This is not mathematically possible and clearly reflects an error. It should be noted that the general population mortality constraint masks the full extent of this error from the model results.

Figure 17: OS predicted by company's model for NMA comparators if HR for OS is set equal to 1.0 and the general population mortality constraint is removed



As a consequence of these two issues, the ERG believes that the results of Base Case Analysis 2 presented in the CS[1] are unreliable.

In response to a further request for clarification from the ERG,[82] the company stated that their approach *"may not have been robust enough"* and rectified these errors as part of an updated version of the model. The results of the ERG-corrected analyses including all comparators are presented in Table 33; these results do not include other minor corrections made by the company during the clarification process.[12]

Table 33: ERG corrected results – Base Case Analysis 1 and 2, fully incremental analysis of pembrolizumab combination therapy and all comparators, deterministic model

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs*	QALYs	Cost	ICER (per QALY gained)
Pembrolizumab combination	5.09	2.95	£72,695	1.61	0.85	£43,389	**£51,240**
Platinum+gemcitabine	3.48	2.11	£29,306	0.89	0.49	£4,572	**£9,401**
Platinum+paclitaxel	2.59	1.62	£24,734	0.62	0.07	£606	**£8,243**
Platinum +docetaxel	2.46	1.55	£24,128	-	-	-	**-**
Carboplatin+paclitaxel/ nab-paclitaxel	1.97	1.27	£24,417	-	-	-	**Dominated**

* *undiscounted*

(ii) Errors relating to the pembrolizumab monotherapy comparison (PD-L1 TPS ≥50% subgroup)

According to Table 40 and text presented on page 99 of the CS,[1] the HR for pembrolizumab combination therapy versus pembrolizumab monotherapy from the ITC is 0.97. Similarly, Figure L.19 in CS Appendix L[11] suggests that pembrolizumab combination therapy is more effective than pembrolizumab monotherapy. However, the company's subgroup analyses suggest that pembrolizumab monotherapy generates 0.46 additional QALYs compared with pembrolizumab combination therapy (see Table 30). The reason for this discrepant result is that within the model, the OS function for pembrolizumab combination therapy is raised to the power of [redacted]. The source of this HR is unclear and is inconsistent with the results of the company's ITC, both in terms of magnitude and direction of effect. The ERG believes that the results of the company's economic comparison of pembrolizumab combination therapy versus pembrolizumab monotherapy within the CS are not valid.

In response to a further request for clarification from the ERG,[82] company applied an HR of 1.03 (1/0.97) as part of an updated version of the model. The corrected results for the PD-L1 TPS ≥50% comparison are summarised in Table 34. The corrected analysis suggests the following: pembrolizumab combination therapy is no longer extendedly dominated; pembrolizumab monotherapy becomes strongly dominated, and the ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel is £25,683 per QALY gained. However, the ERG has further concerns regarding the credibility of this revised conclusion as the cost difference between the two pembrolizumab options is driven by a lower TTD function for combination therapy versus monotherapy. Given that the indirect comparison suggests that PFS and OS outcomes are expected to be worse for pembrolizumab monotherapy, it is unclear why patients would spend more time receiving pembrolizumab as monotherapy than as part of combination therapy. The ERG speculates that this economic finding may be a consequence of variability between patients in the KEYNOTE-407[7, 8] and KEYNOTE-042[17] trials.

Table 34: Company's corrected results for the PD-L1 TPS ≥50% subgroup

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs*	QALYs	Cost	ICER (per QALY gained)
Pembrolizumab combination	3.90	2.86	£64,790	2.12	1.57	£40,388	**£25,683**
Pembrolizumab monotherapy	3.76	2.74	£71,853	-	-	-	**Dominated**
Carboplatin+paclitaxel/ nab-paclitaxel	1.79	1.29	£24,401	-	-	-	-

** undiscounted*

ICER – incremental cost-effectiveness ratio; LYG – life year gained; PD-L1: programmed death-ligand 1; QALY– quality-adjusted life year

(iii) Errors relating to expected costs associated with managing AEs

Within the company's model, the mean cost associated with managing AEs is calculated using the sumproduct of the vectors of AE frequencies and their associated costs, divided through by the sum of the AE frequencies. The ERG believes that the latter part of this calculation reflects an intention to assume that patients can, at most, experience one AE. No justification for this is provided in the CS[1] and the observed AE frequency data from KEYNOTE-407[7, 8] suggest that this assumption is not appropriate: in both arms of the trial, the sum of the AE frequencies exceeds 1.0. The ERG believes that the company's assumption reflects an error, but notes that its impact on the ICER is small.

(iv) Half cycle correction not consistently applied to disease management costs between the options

The calculations of disease management costs are inconsistent between the intervention and comparator groups. For the SC chemotherapy comparator groups in both Base Case Analyses 1 and 2, the calculations of these costs include a half-cycle correction, whilst for the pembrolizumab combination therapy group, the calculations do not include half-cycle correction. The same issue applies within the PD-L1 subgroup analyses. This reflects a further minor error in the model.

(v) Errors in the application of time-to-death utilities

Conceptual issues relating to this aspect of the model are discussed in critical appraisal point (7). With respect to the technical implementation of this approach, the ERG notes that whilst all of the utility values are positive, at a point beyond the end of the time horizon (approximately 36 years), the probability of being in the ≥360 days subgroup becomes negative, hence the QALYs gained in that period also become negative. As this is beyond the time horizon, this issue does not affect the ICER.

(vi) Variation in time to treatment discontinuation parameter for SC chemotherapy linked to a blank cell

Within the overall population and all three PD-L1 subgroups, the model includes a "variation" parameter; this changes the shape of the KM curve for TTD for patients in the SC chemotherapy comparator groups. In each instance, this calculation is linked to a blank cell. This is an unequivocal error which affects the probabilistic analysis of Base Case Analysis 1. Probabilistic results for Base Case Analysis 2 and the subgroup analyses are not reported in the CS.[1]

(2) Unclear interpretation of effectiveness of SC chemotherapy comparators

There is a lack of clarity within the CS[1] regarding the most appropriate comparator(s) for first-line pembrolizumab combination therapy. Two distinct base case analyses are presented within the CS – one using carboplatin plus paclitaxel/nab-paclitaxel (the comparator regimen in KEYNOTE-407[7, 8]) but excluding the other options listed in the NICE scope[6] (Base Case Analysis 1), and one using the comparators listed in the NICE scope (excluding vinorelbine), but excluding the KEYNOTE-407

comparator regimen. Page 136 of the CS states that the company assumed that the regimen used in the control arm of KEYNOTE-407 is equivalent to other platinum-based combination chemotherapy options available in the UK and that clinical experts consulted by the company agreed with this assumption. Given this viewpoint, it is unclear why the second base case analysis using the NMAs is required, as this assumes that the treatment comparators do not have the same level of effectiveness.

The clinical advisors to the ERG stated that in the England, standard treatment would be gemcitabine or vinorelbine plus a platinum drug, but agreed that the company's assumption of equivalent effectiveness between the alternative regimens was reasonable. In response to a request for clarification from the ERG (see clarification response,[12] question B11), the company stated: *"…based on published literature*[9] *and feedback from UK clinical oncologists, it has been assumed that all SoC [standard of care] regimens have the same efficacy in the patient population being assessed in this TA."* The ERG believes that the presentation of results within the CS[1] is somewhat inconsistent and that it would have been more appropriate to either: (a) relegate the comparison against chemotherapy regimens included in the NMA to sensitivity analyses, or (b) include all relevant comparators from KEYNOTE-407[7, 8] and the NMAs within a single fully incremental analysis.

(3) Issues surrounding company's NMAs and ITCs

The ERG has major concerns regarding the NMA and ITC results used in the company's model. The use of a fixed effect NMA and Bucher ITC analysis underestimates the uncertainty in the treatment effect. Furthermore, neither the NMA results for the squamous PD-L1 unselected population nor the ITC results for the PD-L1 TPS ≥50% subgroup used in the company's original submitted model match the results reported in Section B2.9 of the CS.[1] Following the identification of this discrepancy by the ERG, the company presented additional NMAs by combining carboplatin and cisplatin (see clarification response,[12, 82] question B9). Both constant HRs and time-varying HRs NMAs were conducted within the company's additional analyses. The company used the results from the constant HRs fixed effect NMA model without justification. Perhaps most importantly, the validity of the NMAs may be severely compromised as none of the comparator trials included the use of second-line immunotherapy (see Section 4.4). This may contribute to the differences in expected QALY gains between the SC chemotherapy regimens modelled using HRs from the company's NMA.

The ITC analysis for the PD-L1 TPS ≥50% subgroup may have a narrower population than the population defined in the final NICE scope[6] as it excludes patients with untreated brain metastases (see Section 4.4), although the clinical advisors to the ERG noted that these patients are unlikely to be offered pembrolizumab. The ERG also believes that relevant data on patients with squamous NSCLC from KEYNOTE-024[17] should have been included in the analysis, as this study also provides relevant data for the comparison between the pembrolizumab monotherapy and chemotherapy regimens. In the

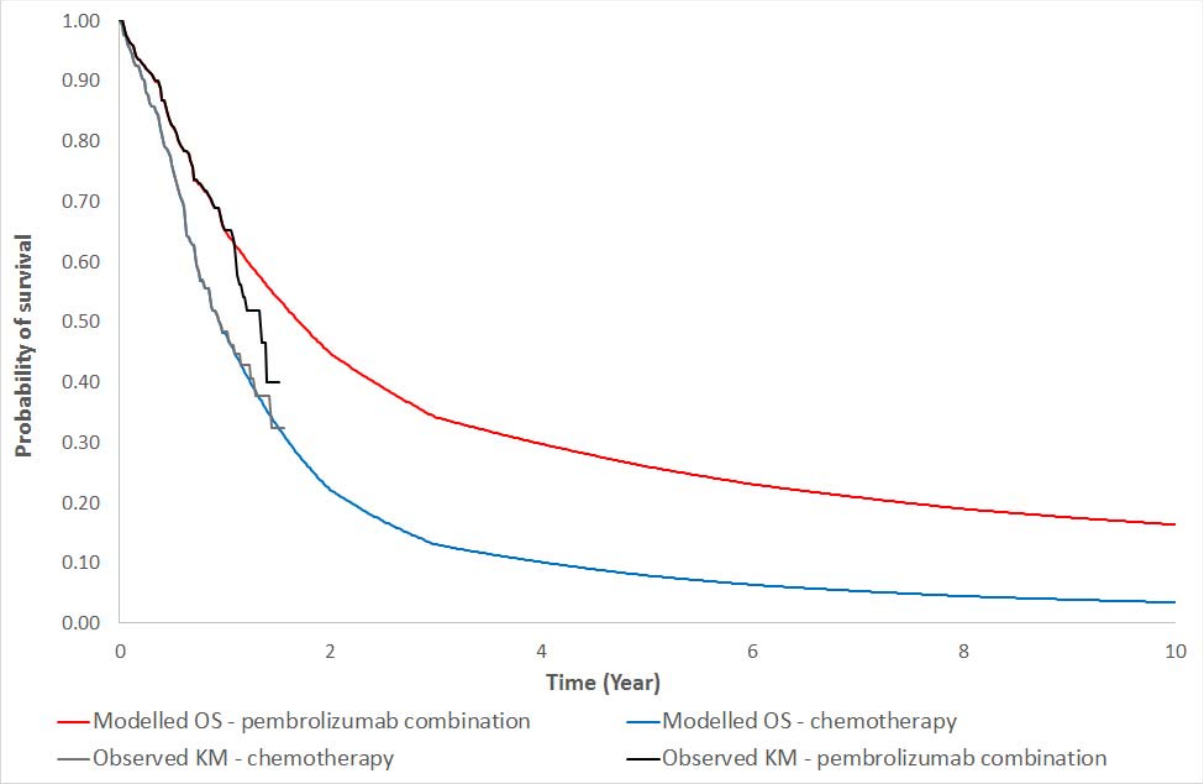
company's clarification response[12] (question A21), various scenario analyses were presented which include KEYNOTE-024[17] in the ITC. However, none of the scenario analysis results presented in the clarification response match the HRs used for OS and PFS for the NMA comparators in the economic model.

(4) Uncertainty surrounding long-term extrapolation

(i) Potentially optimistic extrapolation of OS

The company's model applies external data from SEER[81] to model long-term survival from month 12 onwards, rather than using the observed hazards from KEYNOTE-407[7, 8] to predict future survival. As shown in Figure 18, the available OS data from IA2 of KEYNOTE-407 suggest that it is around this timepoint that the observed KM curves show the greatest degree of separation between the groups. Whilst there are few patients still at risk at month 15 and at later timepoints, the available data suggest that the degree of separation between the curves is decreasing. On the basis of the evidence collected in the trial, this suggests that the company's approach for modelling OS may be optimistic.

Figure 18: Observed and predicted OS curves for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel, company's Base Case Analysis 1



The ERG requested clarification from the company regarding this discrepancy between observed and predicted survival (see clarification response,[12] question B13). In response, the company commented

that "*The data at [the] tail of the KM curve reflect very sparse observations, which from a modeling perspective should be permitted to have little or no impact on the extrapolation regardless of the method used, and this is true of both the parametric and base case population-based (SEER) approaches used. Thus, in the instance of the population-based extrapolation method, there is simply insufficient data to conclude a further trend in OS beyond the period of the KM data modeled.*"

With respect to this argument, the ERG makes the following observations:

- Parametric survival modelling takes into account both events and censored observations in the underlying time-to-event data within the likelihood function. Data should not be discarded simply because they are sparse.
- The company's argument appears to reflect a belief, in a general sense, that it is inappropriate to fit survival models to time-to-event data which are subject to administrative censoring. The ERG disagrees with this viewpoint; at the present time, the best source of information regarding the relative mortality hazard rates in patients with metastatic squamous NSCLC receiving first-line pembrolizumab combination therapy or SC chemotherapy (including currently available second-line immunotherapy) is the observed period of KEYNOTE-407.[7, 8] The ERG also notes that the company's argument for disregarding the available OS data beyond 12-months is inconsistent with their approach for modelling PFS (which involved fitting parametric models to the whole post-26 week dataset from KEYNOTE-407).
- The clinical advisors to the ERG stated that the use of SEER data may be reasonable, but noted that some caution should be exercised, as these data reflect outcomes relating to a different healthcare system.
- Given the immaturity of the data-cut used for IA2, it will be important to revisit the predictions of the model using data from the final analysis of KEYNOTE-407.[7, 8]

(ii) Representativeness of the SEER dataset

The ERG is unaware of any previous appraisals of NSCLC which have directly used data from SEER[81] to model OS. The company's justification for extrapolating OS using SEER data rather than a parametric function fitted to data from KEYNOTE-407[7, 8] is that the mortality risk is time-dependent. Table 59 of the CS shows that the parametric extrapolation does not reflect this trend. However, this argument is weak as the parametric model predictions included in the table relate to the exponential model, which by definition, assumes a constant hazard rate. Alternative parametric models fitted to the KEYNOTE-407 data would have allowed for the incorporation of time-dependent hazard rates.

The CS reference pack includes screenshots of the SEER data request for two distinct periods: 1992-2014 and 2010-2014; it is unclear how the dataset for the third period (years 2000-2014) was

constructed and the actual dataset is not contained within the reference pack. As noted in Section 5.2.4, it is unclear why three datasets covering different time periods were used. Death probabilities from SEER were obtained in 6-month intervals in terms of observed survival using actuarial methods. The population was comprised of patients with Stage IV squamous NSCLC "with malignant behavior" and known age, including cases contained in the research database. Patients without known survival times and those with missing data were excluded.[81] It is unclear if any further population characteristics were available from the dataset. No information is provided regarding the treatments received by the patients contained in the dataset and it is unlikely that any sizeable proportion of patients included in the dataset could have received immunotherapy; this may severely limit the usefulness of the dataset in reflecting current clinical practice in England.

The CS[1] provides a comparison of the UK and US NSCLC populations in order to provide supporting information regarding the appropriateness of using SEER[81] to model long-term OS (data reproduced in Table 35). This information is however limited only to mean patient age at diagnosis and the proportion of males/females in KEYNOTE-407[7, 8] and SEER; additional information from the UK National Lung Cancer Audit 2017/2018 annual report[107] is also provided for comparison. Whilst the company's clarification response[12] acknowledges that there are no comparative data on other relevant characteristics such as type of therapy received, number of previous treatments received and PS, they maintain that the populations *"are not dissimilar to each other"* (clarification response,[12] question B22c). The ERG believes that this conclusion should be approached with caution as these other key characteristics may not be balanced between the data sources. Clinical advisors to the ERG noted that during the period under consideration (1992-2014), US physicians would probably treat the disease more aggressively than UK clinicians and stated that the SEER data are likely to reflect better outcomes than those routinely achieved in the UK. In addition, the ERG notes that the SEER database covers only 18 geographic areas in the US, corresponding to less than 30% of the US population; this may impact on judgements about the comparability of the data sources at the country-level.

Table 35: Comparison of baseline characteristics between KEYNOTE-407,[7, 8] SEER and NCLA (reproduced from the company's clarification response, question B22)

Patients characteristic	KEYNOTE-407[7, 8]	SEER (US)	NLCA (UK)
Median age	65	70	72
% Male	78.3%	65% (2010-14)	58%

SEER - Surveillance, Epidemiology and End Results; NLCA - National Lung Cancer Audit

(iii) Other issues relating to extrapolation

The company's parametric survival modelling uses a piecewise approach with cut-points for OS and PFS determined by the examination of Chow test plots, although the ERG notes that parametric survival models for OS are not used in the company's base case analyses and the PFS functions have no impact on the base case ICERs. The CS[1] does not include any clinical rationale to support the choice of cut-points; within their clarification response[12] (question B19), the company states that there is no further clinical rationale. Chow test plots were based on a linear regression model of the cumulative hazard and time. The ERG notes that it is not meaningful to consider if there is a linear relationship between a cumulative hazard and time. The rejection of a linear relationship does not imply that any of the standard parametric distributions may not be appropriate. During the clarification process, the ERG requested that company provide the empirical hazard plots for OS and PFS (see clarification response,[12] question B16). The company provided the empirical hazard plots for the PD-L1 subgroups in KEYNOTE-407;[7, 8] however, plots were not provided for the ITT population. The ERG believes that there is no evidence to support the use of a piecewise approach for either OS and PFS, and in the case of complex hazard functions, the more flexible models such as the natural cubic spline models by Royston and Parmar (2002)[108] could be used. The ERG also notes that the company's model does not include any uncertainty associated with the observed portion of the piecewise OS models; only uncertainty in the model parameters after the cut-point was considered (see Table 25).

With respect to the extrapolation of TTD, the company fitted standard parametric distributions using a non-piecewise approach. The company used AIC and BIC combined with visual inspection to select the best-fitting curve. The ERG notes that the AIC and BIC statistics were similar in a number of cases and that no sensitivity analysis was provided by the company.

(5) Assumption of lifetime relative risk for OS for pembrolizumab combination therapy versus SC chemotherapy

As described in Section 5.2.2, the company's model assumes an indefinite treatment effect of pembrolizumab combination therapy on OS. This is modelled by applying the RR of death between the treatment groups during months 7-12 within KEYNOTE-407[7, 8] to the SEER mortality probabilities[81] for the comparator group. This RR is applied during each weekly model cycle from the 12-month timepoint for the remainder of the time horizon. Despite the short follow-up duration of IA2 of KEYNOTE-407, the observed KM curves for TTD at IA2 suggest that the probability of remaining on treatment at 15 months is approximately [redacted] and all patients within the trial will discontinue treatment with pembrolizumab by 2 years. Therefore, the company's model assumes that the effect of pembrolizumab on OS persists long after patients have stopped receiving treatment (i.e. a patient who is alive 10 years after discontinuing pembrolizumab is still assumed to have a better survival prognosis

compared with an identical surviving patient who did not receive pembrolizumab). The impact of this RR on OS is shown in Figure 19.

The clinical advisors to the ERG agreed that the assumption of a lifetime treatment effect was likely to be overly optimistic. The advisors noted considerable uncertainty relating to the duration of treatment response and its impact on OS outcomes.

Figure 19: Overall survival for the pembrolizumab combination therapy group including/excluding relative risk for death derived from KEYNOTE-407 months 7-12

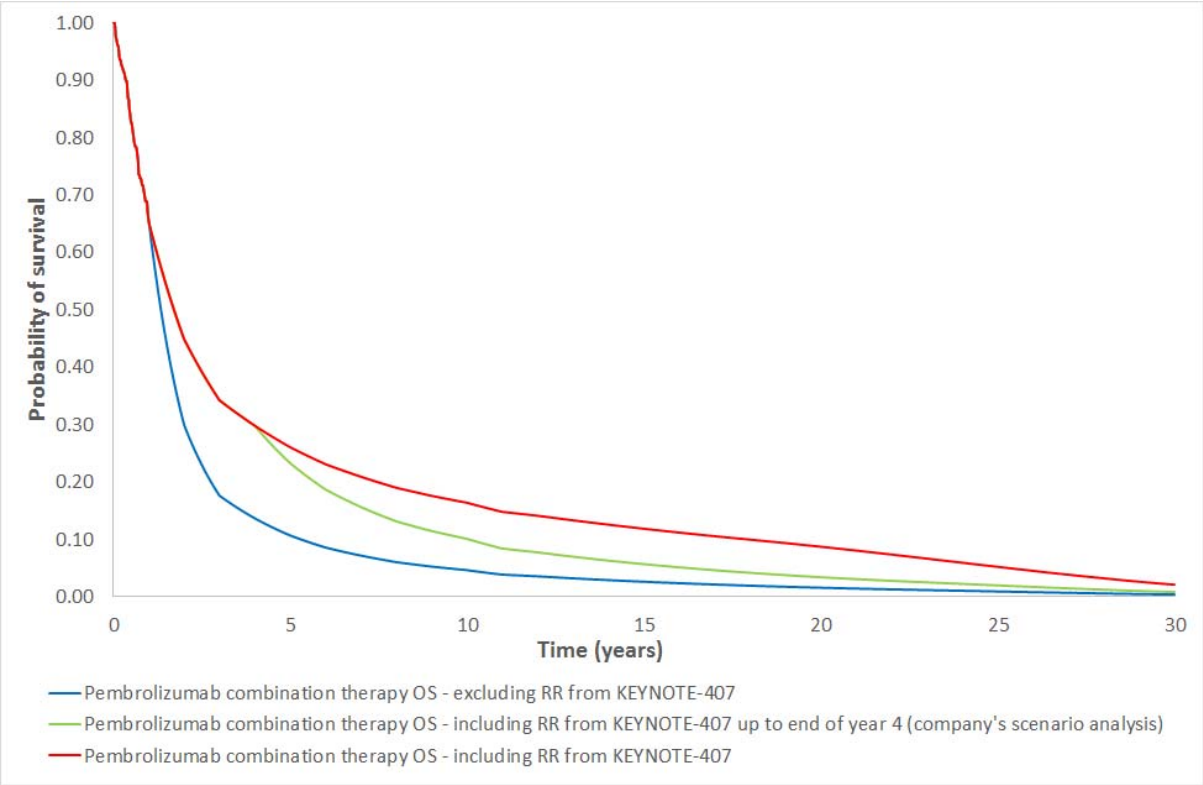


Table 36 shows the impact of assuming that the OS benefits of pembrolizumab combination therapy are lost after 2, 3 or 4 years, based on additional analyses undertaken by the ERG using the company's original submitted model. These analyses indicate that removing the treatment effect for pembrolizumab combination therapy at earlier timepoints increases the ICER considerably.

Table 36: Impact of relaxing company's assumption of lifetime effect, Base Case Analysis 1

Timepoint after which treatment effect is lost	Inc. QALYs	Inc. costs	ICER
Company's base case (lifetime effect)	1.68	£48,278	**£28,672**
2 years	0.76	£40,010	**£52,425**
3 years	1.04	£42,414	**£40,947**
4 years	1.15	£43,444	**£37,730**

QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; inc. - incremental

The company does not discuss the basis of the assumption of an indefinite treatment effect in detail within the CS.[1] Table 56 of the CS states that *"there is no evidence that treatment effect stops after discontinuation."* However, the CS does not provide any information regarding any analyses of the KEYNOTE-407[7, 8] data that have been performed to support this view.

As part of the clarification process, the ERG asked the company to provide evidence to support the assumption of a continued treatment effect beyond discontinuation. In their response, the company stated *"There is no evidence to suggest that discontinuing pembrolizumab at 2 years does lead to a loss of treatment effect. MSD have previously provided scenarios in which treatment waning is investigated from year 5 (scenario 9 of the CS). Data from a publication from Herbst et al[109] investigating long-term survival of patients with advanced NSCLC in KEYNOTE-010 who completed 2 years of treatment with pembrolizumab. It concluded that most patients who completed 35 cycles or 2 years of pembrolizumab therapy had durable response, with ongoing response in 64% of patients at median follow-up of 43.4 months"* (clarification response,[12] question B12). For the sake of clarity, the ERG notes that the company's scenario analysis assumes the loss of treatment effect after 4 years, rather than a waning of effect. The company's clarification response does not provide much additional information over and above that provided in the CS.[1] The ERG notes that KEYNOTE-010 enrolled a different patient population to KEYNOTE-407 (previously treated and PD-L1 positive [TPS≥1%]) and included only pembrolizumab monotherapy; OS outcomes may be different for patients with untreated squamous metastatic NSCLC receiving pembrolizumab combination therapy. The ERG also notes that the published abstract by Herbst *et al*[109] states that response was ongoing in 59% of patients who had received 35 cycles of pembrolizumab and that median follow-up in the overall study was 42.5 months; it is unclear which data the company's clarification response refers to.

The ERG also has concerns regarding the use of an RR as the measure for the relative treatment effect on OS as this relates only to a specific time interval (7-12 months). For time-to-event data, the use of an HR would be a more appropriate measure as this takes into account the time at which an event occurs. Given that the company performed NMAs using time-varying HRs, it is unclear why these results were not used to model effects on OS.

Given the short follow-up from IA2 of KEYNOTE-407,[7, 8] the ERG believes that it is unknown whether or for how long the effects of pembrolizumab combination therapy on OS are maintained after treatment discontinuation in patients with metastatic squamous NSCLC. This is a key area of uncertainty which may be resolved through additional follow-up in KEYNOTE-407.

The ERG notes that these issues do not apply when OS is modelled using standard parametric survival curves; however, the CS[1] only reports two sensitivity analysis using this approach (KM/exponential and

KM/log logistic). Table 37 presents the results of additional analyses undertaken by the ERG which use all of the company's fitted piecewise parametric models for OS (assuming a 19-week cut-off). As shown in the table, the company's base case ICER is considerably lower than all alternative OS models.

Table 37: Impact of company's alternative piecewise parametric OS functions, 19-week cut-point, Base Case Analysis 1

Option	Absolute			Incremental			
	LYGs*	QALYs	Cost	LYGs‡	QALYs	Cost	ICER (per QALY gained)
Exponential							
Pembrolizumab combination	1.95	1.36	£58,483	0.65	0.46	£36,989	**£80,142**
Carboplatin+paclitaxel/ nab-paclitaxel	1.30	0.90	£21,494	-	-	-	-
Weibull							
Pembrolizumab combination	1.99	1.39	£58,705	0.65	0.46	£36,999	**£80,532**
Carboplatin+paclitaxel/ nab-paclitaxel	1.34	0.93	£21,706	-	-	-	-
Log normal							
Pembrolizumab combination	5.29	3.06	£73,678	2.18	1.17	£44,368	**£37,761**
Carboplatin+paclitaxel/ nab-paclitaxel	3.11	1.89	£29,311	-	-	-	-
Log logistic							
Pembrolizumab combination	3.96	2.40	£67,706	1.47	0.84	£41,053	**£48,706**
Carboplatin+paclitaxel/ nab-paclitaxel	2.50	1.55	£26,653	-	-	-	-
Gompertz							
Pembrolizumab combination	1.49	1.05	£55,788	-0.09	-0.01	£33,018	**Dominated**
Carboplatin+paclitaxel/ nab-paclitaxel	1.58	1.06	£22,770	-	-	-	-
Generalised gamma							
Pembrolizumab combination	1.39	0.98	£55,222	0.08	0.07	£33,638	**£485,108**
Carboplatin+paclitaxel/ nab-paclitaxel	1.31	0.91	£21,584	-	-	-	-

** LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio*

(6) Inclusion of an implicit assumption of cure

The company's model includes a general population mortality constraint which ensures that the probability of death predicted by the KM/SEER OS model during each cycle is never lower than the mortality risk in the general population. Within the modelled pembrolizumab combination therapy group, this constraint begins to take effect at week 940 (approximately 18 years) and applies to every subsequent model cycle beyond this timepoint; at this point, 9.9% of intervention group patients are

still alive. Within the carboplatin plus paclitaxel/nab-paclitaxel comparator group (Base Case Analysis 1), the constraint begins to take effect at week 1,201 (approximately 23 years) and applies to every subsequent model cycle beyond this timepoint; at this point, around 0.8% of comparator group patients are still alive. This reflects an implicit assumption of cure, as patients surviving up to this point are assumed to have no excess risk of death due to their NSCLC. The plausibility of this model prediction, and its interpretation as a cured proportion predicted by the model, is not discussed in the CS.[1] The ERG notes that KEYNOTE-407[7, 8] does not provide any evidence to support the assumption that pembrolizumab combination therapy can provide a cure for patients with untreated squamous metastatic NSCLC.

During the clarification process, the ERG asked the company to comment on the plausibility of the predicted 9.9% of pembrolizumab-treated patients who achieve a cure. In response, the company stated *"…>9.9% of patients annually must have died within the general population around year 18, for that to have over-ridden the SEER extrapolated risk. This can be considered plausible, as the general population risks account for increasing mortality with age, whereas for SEER there was not enough data to model mortality precisely beyond year 13 and therefore the constant 9.9% risk is a valid assumption"* (clarification response,[12] question B30d). The ERG considers the company's response to be unclear – it appears that the company is referring to both the 9.9% of the modelled cohort receiving pembrolizumab combination therapy who are estimated to be cured in the model trace and the annual mortality risk of 9.9% from year 13 onwards in the SEER data (applied to the carboplatin plus paclitaxel/nab-paclitaxel group). The ERG speculates that the fact that these two values have a value of 9.9% is a coincidence and notes that the company's response provides no further justification regarding the assumption of cure within the model.

(7) Concerns regarding the company's approach to modelling HRQoL

(i) Concerns regarding the reliability of the time-to-death approach

The company's model uses a time-to-death approach for modelling HRQoL, based on four categories. The CS[1] justifies the use of this approach on the basis that:

- It reflects the known decline in cancer patients' HRQoL during the terminal phase of the disease.
- It has been previously used in the estimation of HRQoL in patients with advanced NSCLC who had previously received platinum-based chemotherapy or palliative radiotherapy and in advanced melanoma patients.
- It has been demonstrated to be more relevant than progression-based utilities as it offers a better data fit.[1]

The ERG's clinical advisors commented that the use of a time-to-death approach is reasonable; however, one advisor also commented that disease progression is a key determinant of patients' HRQoL. Despite its precedents in previous NICE technology appraisals (including pembrolizumab monotherapy[83]), published economic models[110] and published HRQoL valuation studies,[111-113] the ERG has some concerns regarding the company's approach.

(i) Potential overestimation of HRQoL for patients in longer time-to-death categories

Patients with a time-to-death ≥360 days or 180 to 360 days are assigned utility scores of [redacted] and [redacted], respectively. These values are similar to the sex-adjusted general population utility value for individuals aged 65-74 years based on Ara and Brazier[98] (estimated utility = 0.79). The model may therefore overestimate HRQoL for patients in these time-to-death categories, given that the population has metastatic NSCLC (some of whom may have progressed disease).

(ii) Potential overestimation of HRQoL for patients with longer time-to-death

In KEYNOTE-407,[7, 8] the EQ-5D-3L was administered at each of the first 7 treatment cycles, then every third cycle (9 weeks), for up to 48 weeks whilst patients were receiving treatment; the questionnaire was also administered at a treatment discontinuation visit and at the 30-day post treatment safety follow-up visit.[1] Whilst part of the company's rationale for adopting the time-to-death approach was to capture the decline in HRQoL during the terminal phase of the disease, the design of the trial means that EQ-5D assessments for patients with progressed disease will have been undertaken only shortly after disease progression was established (at most, 30 days later). Consequently, the ERG considers there to be a strong possibility that the available EQ-5D data for progressed patients are subject to bias due to informative censoring. According to the company's model predictions, more than half of the patients' survival time is spent in the post-progression state in both treatment groups, yet the EQ-5D data relate only to the beginning of this phase. Given the limitations of the EQ-5D data collection process in KEYNOTE-407, which is similar to many other trials of oncology products, the ERG has doubts that the time-to-death provides a robust approach for reflecting HRQoL for patients in the later stages of the disease. The ERG also notes that the same potential bias would apply to the use of progression-based utilities based on KEYNOTE-407. For this reason, the ERG believes there is value in exploring the use of other health valuation studies which are less likely to be subject to this issue (for example, Khan *et al*[114] and Chouaid *et al* 2013[115]).

(iii) Unclear rationale for including ratio multipliers for pembrolizumab monotherapy

Within the company's subgroup analyses of patients with PD-L1 TPS ≥50%, the utilities applied in each time-to-death category are different for the pembrolizumab monotherapy group compared with the other treatment groups (based on relative utility ratios). In addition, a constraint is applied to limit

HRQoL for patients in the time-to-death group ≥360 days to [redacted] in the pembrolizumab monotherapy group. No justification is provided for these assumptions and their underlying rationale is unclear.

(8) Uncertainty surrounding use second-line immunotherapy in the SC chemotherapy groups

The ERG believes that the costs associated with second-line treatments may be unreliable, particularly with respect to those applied in the SC chemotherapy comparator groups. As these costs are based on IA2 of KEYNOTE-407,[7, 8] it is possible that the proportion of patients going on to receive second-line immunotherapy will increase with additional follow-up. In response to a request for clarification from the ERG[12] (question B34), the company noted that the extent to which this proportion would increase in later data-cuts is unknown and any increase would likely have a favourable impact on the ICER for pembrolizumab combination therapy due to the higher costs of second-line immunotherapy which apply only to the SC chemotherapy comparator groups. The ERG agrees with the company's view that their base case ICERs are likely to be pessimistic in this respect; however, the greater use of second-line immunotherapy in the comparator group may also lead to additional OS benefits. The overall impact of this issue on the cost-effectiveness of pembrolizumab combination therapy is unclear.

The ERG also notes that the use of an interim analysis presents issues for estimating the duration of treatment on second-line regimens. It is unclear from the company's model, the CS[1] and the CS appendices[11] how these treatment durations have been estimated, whether they are means or medians, and how censoring has been dealt with. The ERG also notes that within NICE TA428[89] (pembrolizumab for previously treated PD-L1 positive NSCLC), the mean PFS time in the company's model, which was used as a proxy for time on treatment, appears to be around 7 months; this is considerably greater than the mean treatment time for second-line immunotherapy assumed in the company's model for this appraisal (approximately [redacted] months). This suggests that the costs incurred by those patients who go on to receive second-line treatment in the company's model may be underestimated.

These uncertainties may be resolved through the additional follow-up in KEYNOTE-407.[7, 8]

(9) Clinically unrealistic assumptions regarding disease management costs

Within the company's model, costs related to the management of the disease are defined according to progression status, but are applied according to TTD and the probability of receiving second-line treatment. PFS costs are applied to patients whilst receiving first-line treatment and indefinitely for those who receive second-line treatment, whereas post-progression costs are applied to patients who discontinued first-line treatment but do not receive second-line treatment. Clinical advisors to the ERG noted that disease management costs change following disease progression e.g. due to increased

hospital admissions. As such, the ERG considers that the company's approach is arbitrary and is unlikely to reflect the nature of resource use for patients with metastatic squamous NSCLC.

(10) Issues relating to AEs

The company's model estimates HRQoL decrements associated with Grade 3-5 AEs based on the difference between the EQ-5D valuation for patients who were progression-free with Grade 3-5 AEs and those who were progression-free without Grade 3-5 AEs in KEYNOTE-407.[7, 8] The QALY loss associated with AEs is calculated using this disutility, together with the frequency of AEs in each treatment group and the mean duration of AEs. The ERG believes that this approach may understate the differences in HRQoL impacts between the treatment groups:

(i) It has been discussed within the literature[116] that checkpoint inhibitors such as pembrolizumab have a different toxicity profile than chemotherapy. For example, pembrolizumab has been shown to be associated with immune-related endocrinopathies (such as hyper/hypothyroidism, Type I diabetes mellitus, diabetic ketoacidosis), gastrointestinal events (e.g. colitis), respiratory events (e.g. pneumonitis) and hepatotoxicities. These AEs may have long-term impacts and may require long-term treatment. The company's approach allows for differences in AE frequency between treatment groups, but assumes that AEs have the same magnitude of impact on HRQoL and the same duration, irrespective of treatment group. This may not adequately reflect the true health impact associated with immune-related AEs, which can be lifelong and can occur later than chemotherapy-related AEs.

(ii) Given that the KEYNOTE-407 data[7, 8] are based on an interim analysis, the complete AE profile associated with pembrolizumab combination therapy may not yet have been established within the trial.

(iii) AEs may have manifested in patients with progressed disease; however, EQ-5D estimates for these patients are not used to value the disutility associated with AEs within the company's model.

5.4 Exploratory analyses undertaken by the ERG

This section presents the methods and results of the ERG's exploratory analyses undertaken using the company's model.

5.4.1 ERG's exploratory analyses - methods

Additional survival analysis undertaken by the ERG

In order to inform the ERG's exploratory analyses, the ERG undertook additional survival analyses using the time-to-event data from KEYNOTE-407.[7, 8] The ERG reconstructed individual patient-level data (IPD) for each treatment arms in KEYNOTE-407 for both OS and PFS using the algorithm proposed by Guyot *et al.*[117] A range of models were fitted to the data including both standard parametric

models (exponential, Weibull, log logistic, log normal, Gompertz, gamma and generalised gamma) and natural cubic spline models[108] with knots=[1, 2, 3] based on modelling the log of the cumulative hazard function. The IPD were reconstructed using the reported KM data contained in the economic model directly, rather than by digitising the KM curves. The ERG used the *flexsurv* package in R[118] for all survival analyses. The ERG's analyses used all of the observed data from KEYNOTE-407, rather than the piecewise approach adopted by the company, as neither the data nor clinical opinion supported the company's use of cut-points. Goodness-of-fit statistics (AIC and BIC) and survivor functions for the ERG's survival analyses are summarised in Appendix 3.

Overview of ERG exploratory analysis

The ERG undertook four initial sets of exploratory analyses within the overall squamous NSCLC population using the company's original submitted model; these are based on the direct comparison of pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel (company's Base Case Analysis 1). These initial analyses involved correcting errors identified in the company's model, converting the company's model to adopt a progression-based approach for HRQoL and disease management costs and increasing the duration of second-line immunotherapy. In addition, the ERG applied alternative PFS and OS models which were consistent with the outcomes expected by the ERG's clinical advisors; taken together, these model amendments form the ERG's preferred analyses. One of the clinical advisors suggested different expected OS estimates to the other two clinicians, hence the ERG's preferred analyses are presented across two scenarios: (i) an optimistic scenario and (ii) a pessimistic scenario. The optimistic scenario uses OS models estimated by the company, whilst the pessimistic scenario uses OS models fitted by the ERG.

Sensitivity analyses were undertaken using the ERG's preferred models to explore the impact of alternative choices around HRQoL parameters and the usage of second-line therapy. Further sensitivity analyses were also undertaken to explore the impact of applying the full range of alternative ERG-fitted OS models fitted to the KEYNOTE-407 data.[7, 8]

An exploratory sensitivity analysis was also undertaken to explore the impact of optimistic and pessimistic PFS/OS projections on the cost-effectiveness of pembrolizumab combination therapy versus the standard chemotherapy comparator regimens from the company's NMAs.

Exploratory analyses were also undertaken for the PD-L1 subgroups, based on the assumptions employed in the ERG's preferred analyses.

All analyses were undertaken using the deterministic version of the company's model, based on first model revision received by the ERG following the clarification process. Implementation of the ERG's

exploratory analyses was repeated by a second modeller to ensure that the results are free from errors. Technical details regarding the implementation of these analyses in the company's model are presented in Appendix 4.

The following sections detail the specific changes applied within each analysis.

ERG's exploratory analysis 1: Correction of errors

The ERG's double-programming exercise identified several errors in the company's submitted model. The following errors were corrected by the ERG:

(a) *Correction of OS functions for NMA comparators*. The OS curves for the NMA comparators were estimated by raising the cumulative survival probabilities for the pembrolizumab combination therapy group to the power of the relevant HRs from the NMA. This correction does not affect the ERG's preferred analyses in the overall squamous NSCLC population.

(b) *Correction of the HR for OS for the pembrolizumab monotherapy comparison (PD-L1 TPS ≥50% subgroup)*. The HR for pembrolizumab monotherapy versus pembrolizumab combination therapy was set equal to 1.03. This correction impacts only on the ERG's exploratory subgroup analyses.

(c) *Amendment of AE cost calculations*. The company's AE cost calculations were amended to remove the assumption that patients can experience only one event.

(d) *Consistent application of half-cycle correction*. The model was amended to include half-cycle correction for all treatment options.

ERG's exploratory analysis 2: Use of HRQoL based on progression status

As noted in Section 5.3.3, the ERG believes that the company's time-to-death approach for modelling HRQoL may be unreliable due to limited data collection in patients following disease progression in KEYNOTE-407.[7, 8] In response to a request for clarification,[12] (question B7d) the company presented information relating to three studies identified by their HRQoL searches which defined health utilities according to progression status.[115, 119, 120] The ERG believes that the value reported by Khan *et al*[119] (based on the TOPICAL trial[121]) may be the most relevant estimate of post-progression utility as: (i) this trial included collection of HRQoL data in progressed patients; (ii) HRQoL was measured using the EQ-5D, and (iii) few patients in the placebo group received active therapy after disease progression, hence the estimate is unlikely to be contaminated by post-progression treatments. Within the ERG's analysis, HRQoL for patients with progressed disease was based on the reported EQ-5D estimate for the placebo group of TOPICAL (post-progression utility=0.58), whilst HRQoL for the progression-free state was based on KEYNOTE-407 [redacted] As a proportion of patients in each treatment group of KEYNOTE-407 received second-line treatment, the ERG's analysis assumes that patients who progress on first-line treatment and subsequently receive second-line

treatment will spend additional time with improved HRQoL. The proportion of remaining survival time spent in a progression-free state (after progression on first-line treatment) was based on estimates of progression-free and post-progression sojourn time from the model developed to inform NICE TA428[89] (using information reported in Table 100 of the company's submission for this appraisal; note – only discounted estimates were available). Within each of the modelled treatment groups, additional post-progression HRQoL benefits were applied as follows:

(i) Patients receiving second-line chemotherapy– 49% of remaining survival time assumed to be spent in progression-free state
(ii) Patients receiving second-line immunotherapy - 32% of remaining survival time assumed to be spent in progression-free state
(iii) Patients not receiving second-line treatment – no additional PFS time, post-progression utility applied for remaining survival time.

ERG's exploratory analysis 3: Disease management costs based on PFS/PPS

The ERG has concerns that the company's approach to modelling disease management costs does not reflect clinical reality. Within this exploratory analysis, disease management costs were applied according to the presence/absence of disease progression. As with the ERG's approach used to model progression-based HRQoL, post-progression costs were weighted to account for additional PFS time for those patients who receive second-line treatment; this adjustment was based on the same assumptions as those used in ERG exploratory analysis 2.

ERG's exploratory analysis 4: Second-line immunotherapy treatment costs doubled

The ERG believes that the assumed treatment durations for second-line immunotherapy from KEYNOTE-407 applied in the company's model are likely to be underestimates. Within this analysis, the treatment duration for second-line immunotherapy was doubled; this better reflects the treatment duration assumed in NICE TA428.[89]

ERG's exploratory analysis 5a and 5b: Alternative PFS and OS models

As noted in Section 5.3.3, the ERG has concerns that the company's PFS and OS predictions may be optimistic. In order to address this concern, the ERG's clinical advisors were asked to estimate PFS and OS probabilities at 5, 10 and 20 years for patients receiving pembrolizumab combination therapy and for patients receiving SC chemotherapy (taking into account those patients receiving second-line pembrolizumab monotherapy, based on IA2 in KEYNOTE-407[7, 8]). The clinical advisors noted considerable uncertainty given the short follow-up duration from IA2 of KEYNOTE-407 and found this task very difficult to complete.

Clinicians' and ERG's estimates of OS

With respect to OS, two of the clinical advisors preferred the projections of the company's KM/log logistic model for the pembrolizumab combination therapy group (5-year OS probability = 20%; 10-year OS probability = 11%) and the KM/SEER model for the SC chemotherapy group (5-year OS probability = 8%; 10-year OS probability = 3%). The ERG notes that the KM/log logistic model suggests that 6% of patients treated with pembrolizumab combination therapy will achieve cure by 18 years (no excess risk of mortality due to NSCLC).

The third clinical advisor suggested estimates of OS for the pembrolizumab combination therapy group of 15-20% at 5 years, 5-10% at 10-years and <2% at 20 years. The advisor noted that their preferred OS estimates for this group would likely lie between the ERG's log logistic and exponential functions. For the SC chemotherapy group, the clinician suggested OS estimates of 8-10% at 5 years and around 5% at 10 years (including second-line pembrolizumab monotherapy use). Based on this information, the ERG has assumed the log logistic function (fitted by the ERG using the whole KEYNOTE-407 dataset) for both treatment groups, but notes that this is favourable to the pembrolizumab combination therapy group.

Clinicians' and ERG's estimates of PFS

Two of the clinical advisors believed that the company's piecewise log normal PFS models were reasonable; these models indicate 5-year PFS probabilities for the pembrolizumab combination therapy and the SC chemotherapy groups of 0.10 and 0.03, respectively. The third clinical advisor also believed that the estimates from this model were plausible, but noted difficulty in estimating long-term PFS.

Optimistic and pessimistic scenarios presented as part of the ERG's exploratory analyses

Owing to uncertainty in the clinical evidence, the ERG presents two sets of analysis: (a) an optimistic analysis based on the views of Clinicians 1 and 2, and (b) a pessimistic analysis based on the views of Clinician 3. The PFS and OS models applied in these analyses are summarised in

Table 38.

Table 38: PFS and OS models used in ERG's preferred optimistic and pessimistic analyses

Model	Optimistic analysis – Exploratory analysis 5a	Pessimistic analysis - Exploratory analysis 5b
OS model - pembrolizumab combination therapy	Company's KM/log logistic model (19-week cut-point)	ERG's log logistic model* (no cut-point)
OS model - SC chemotherapy	Company's KM/SEER model (19-week cut-point)	ERG's log logistic model* (no cut-point)
PFS model - pembrolizumab combination therapy	Company's piecewise log normal model (26-week cut-point)	Company's piecewise log normal model (26-week cut-point)
PFS model – SC chemotherapy	Company's piecewise log normal model (26-week cut-point)	Company's piecewise log normal model (26-week cut-point)

OS - overall survival; PFS- progression-free survival; KM - Kaplan-Meier; SEER - Surveillance, Epidemiology and End Results; ERG - Evidence Review Group
** These models broadly approximate the clinician's expected OS as 5-years*

The assumed OS curves applied in each scenario are presented in Figure 20; the clinicians' preferred PFS curves are based on the company's projections (previously shown in Figure 11).

Figure 20: ERG-preferred optimistic and pessimistic OS models and company's base case OS models (excludes general population mortality constraint) – Figure redacted due to AIC

ERG's exploratory analysis 6a and 6b: ERG-preferred analysis

This analysis combines ERG exploratory analyses 1-5 for the optimistic and pessimistic scenarios.

Additional sensitivity analysis 1: Increased proportion costs of second-line immunotherapy

Within this analysis, the proportion of patients in both treatment groups who are assumed to receive second-line treatment was arbitrarily increased to 75%.

Additional sensitivity analysis 2: Impacts of AEs on HRQoL and costs doubled for pembrolizumab combination therapy group

Within this analysis, the costs and QALY losses applied in the pembrolizumab combination therapy group were doubled.

Additional sensitivity analysis 3: Fully incremental analysis including NMA comparators

This analysis includes the three additional SC chemotherapy options from the company's NMA3 (cisplatin/carboplatin in combination with docetaxel, gemcitabine or paclitaxel). Owing to the ERG's concerns regarding the absence of second-line immunotherapies in the trials included in the company's NMAs, the results of this analysis should be interpreted with caution.

Additional sensitivity analysis 4: Exploration of all parametric models fitted by the ERG

Within this analysis, all standard parametric models and spline models fitted by the ERG were considered, assuming the same functional form for both treatment groups.

Additional sensitivity analysis 5: Subgroup analyses by PD-L1 subgroup

Additional subgroup analyses were performed based on the OS model choices adopted in the ERG's preferred analyses (ERG exploratory analyses 6a and 6b).

5.4.2 ERG's exploratory analyses - results

ERG's preferred analyses - overall squamous NSCLC population

The results of the ERG's preferred analyses are presented in Table 39. The results are presented as individual changes relative to the ERG's corrected model (ERG exploratory analysis 1); all individual changes are combined in ERG exploratory analyses 6a and 6b.

The analyses indicate that the correction of model errors, the use of progression-based HRQoL and costs and an assumed increase in second-line immunotherapy costs do not have a substantial impact on the ICER (ERG exploratory analyses 1-4). However, the assumptions regarding OS in each treatment group are key drivers of the ICER (ERG exploratory analysis 5). Under the ERG's preferred optimistic scenario, the ICER for pembrolizumab combination therapy versus SC chemotherapy is estimated to be

£35,981 per QALY gained; under the ERG's preferred pessimistic scenario, the ICER is estimated to be £49,473 per QALY gained.

Table 39: Results of ERG-preferred analysis, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's base case							
Pembrolizumab combination	5.09	2.95	£72,695	3.12	1.68	£48,278	**£28,672**
Standard chemotherapy	1.97	1.27	£24,417	-	-	-	-
ERG exploratory analysis 1 - Correction of errors†							
Pembrolizumab combination	5.06	2.94	£72,806	3.09	1.68	£48,093	**£28,693**
Standard chemotherapy	1.97	1.27	£24,713	-	-	-	-
ERG exploratory analysis 2 - Use of HRQoL based on progression status (includes ERG corrections)							
Pembrolizumab combination	5.06	2.58	£72,806	3.09	1.42	£48,093	**£33,860**
Standard chemotherapy	1.97	1.16	£24,713	-	-	-	-
ERG exploratory analysis 3 - Disease management costs based on PFS/PPS							
Pembrolizumab combination	5.06	2.94	£71,243	3.09	1.68	£46,465	**£27,722**
Standard chemotherapy	1.97	1.27	£24,779	-	-	-	-
ERG exploratory analysis 4 - Second-line immunotherapy treatment costs doubled							
Pembrolizumab combination	5.06	2.94	£72,806	3.09	1.68	£43,250	**£25,804**
Standard chemotherapy	1.97	1.27	£29,555	-	-	-	-
ERG exploratory analysis 5a -ERG optimistic PFS and OS curves							
Pembrolizumab combination	3.94	2.39	£67,846	1.98	1.12	£43,133	**£38,438**
Standard chemotherapy	1.97	1.27	£24,713	-	-	-	-
ERG exploratory analysis 5b ERG pessimistic PFS and OS curves							
Pembrolizumab combination	3.23	2.04	£64,724	1.06	0.64	£39,012	**£60,601**
Standard chemotherapy	2.17	1.40	£25,712	-	-	-	-
ERG exploratory analysis 6a - ERG preferred analysis - optimistic							
Pembrolizumab combination	3.94	2.17	£66,008	1.98	1.01	£36,387	**£35,981**
Standard chemotherapy	1.97	1.16	£29,621	-	-	-	-
ERG exploratory analysis 6b -ERG preferred analysis - pessimistic							
Pembrolizumab combination	3.23	1.91	£62,832	1.06	0.65	£32,050	**£49,473**
Standard chemotherapy	2.17	1.26	£30,782	-	-	-	-

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted; † Analyses 2-6 each include error corrections from analysis 1*

Additional sensitivity analyses - overall squamous NSCLC population

Table 40 presents the results of the ERG's additional sensitivity analyses around use of second-line treatment and increased AE impacts for pembrolizumab combination therapy using the ERG's preferred optimistic and pessimistic scenarios. As shown in the table, the potential for increased use of second-line therapy at later data-cuts of the KEYNOTE-407 trial may lead to reductions in the ICER for pembrolizumab combination therapy. The table also indicates that the model is not sensitive to assumptions regarding AE impacts associated with pembrolizumab, although the full economic impact of IRAEs remains unclear.

Table 40: Results of additional sensitivity analyses using the ERG-preferred analysis, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel

	ERG preferred analysis - optimistic scenario			ERG preferred analysis – pessimistic scenario		
	Inc. QALYs	Inc. costs	ICER	Inc. QALYs	Inc. costs	ICER
ERG's preferred analysis	1.01	£36,387	**£35,981**	0.65	£32,050	**£49,473**
Sensitivity analysis 1 – 75% patients receive second-line treatment	1.05	£32,333	**£30,676**	0.67	£28,311	**£42,280**
Sensitivity analysis 2 – AE QALY loss and costs doubled	1.00	£37,889	**£37,851**	0.64	£33,552	**£52,627**

Table 41 presents the results of the ERG's preferred analyses including the comparators from the company's NMAs together with the comparator regimen included in KEYNOTE-407. These analyses suggest that carboplatin+paclitaxel/nab-paclitaxel is strongly dominated and the ICER for pembrolizumab combination therapy versus the next most effective option (cisplatin/carboplatin plus gemcitabine) ranges from £51,054 to £56,831 per QALY gained. These results should be interpreted with caution due to the ERG's concerns regarding the reliability of the company's NMAs.

Table 41: Sensitivity analysis 3 – fully incremental analysis of all options using the ERG's preferred optimistic and pessimistic models

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG-preferred analysis – optimistic, pembrolizumab combination versus all comparators (deterministic)							
Pembrolizumab combination	3.94	2.17	£66,008	1.27	0.68	£34,866	**£51,054**
Platinum+gemcitabine	2.67	1.49	£31,142	0.66	0.31	£3,733	**£11,891**
Platinum+paclitaxel	2.01	1.18	£27,408	0.10	0.05	£470	**£9,021**
Carboplatin+paclitaxel/ nab-paclitaxel	1.97	1.16	£29,621	-	-	-	**Dominated**
Platinum+docetaxel	1.91	1.12	£26,938	-	-	-	**-**
ERG-preferred analysis – pessimistic, pembrolizumab combination versus all comparators (deterministic)							
Pembrolizumab combination	3.23	1.91	£62,832	1.01	0.59	£33,515	**£56,831**
Platinum+gemcitabine	2.22	1.32	£29,317	0.50	0.26	£3,138	**£12,126**
Carboplatin+paclitaxel/ nab-paclitaxel	2.17	1.26	£30,782	-	-		**Dominated**
Platinum+paclitaxel	1.72	1.06	£26,179	0.07	0.04	£380	**£8,697**
Platinum+docetaxel	1.65	1.02	£25,799	-	-	-	**-**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; PD-L1 - programmed death-ligand 1; QALY - quality-adjusted life year
** - undiscounted*

Table 42 presents the results of the ERG's sensitivity analyses around alternative OS functions. These analyses suggest that the ICER ranges from £35,981 to £274,028 per QALY gained. Importantly, these analyses indicate that a number alternative OS functions lead to ICERs which are considerably higher than those included in the company's base case analysis and the ERG's preferred scenarios. The ERG notes that some of this uncertainty may be resolved through longer data collection in KEYNOTE-407.

Table 42: Sensitivity analysis 4 – alternative ERG-fitted OS models applied to the ERG's preferred optimistic and pessimistic models, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel

OS model (both treatment groups)	Inc. QALYs	Inc. Costs	ICER
ERG preferred model - optimistic	1.01	£36,387	**£35,981**
ERG preferred model - pessimistic	0.65	£32,050	**£49,473**
Generalised gamma	0.12	£28,947	**£233,327**
Gamma	0.41	£30,994	**£76,057**
Log normal	0.81	£33,968	**£42,193**
Log logistic	0.65	£32,050	**£49,473**
Weibull	0.36	£30,697	**£84,320**
Gompertz	0.20	£29,575	**£144,595**
Exponential	0.53	£31,961	**£60,302**
Spline k=1,scale=hazard	0.33	£30,470	**£91,995**
Spline k=2,scale=hazard	0.22	£29,506	**£135,956**
Spline k=3,scale=hazard	0.10	£28,363	**£274,028**
Spline k=1,scale=normal	0.63	£32,579	**£51,611**
Spline k=2,scale=normal	0.39	£30,698	**£78,446**
Spline k=3,scale=normal	0.25	£29,114	**£116,905**
Spline k=1,scale=odds	0.58	£31,851	**£54,645**
Spline k=2,scale=odds	0.39	£30,408	**£78,200**
Spline k=3,scale=odds	0.22	£28,215	**£130,059**

Inc. – incremental; OS – overall survival; ICER – incremental cost-effectiveness ratio; k=knot

ERG's preferred analyses – exploratory subgroup analyses

Table 43 and Table 44 present the results of the ERG's exploratory subgroup analyses for the ERG's preferred optimistic and pessimistic scenarios, respectively. It should be noted that these analyses should be considered as exploratory due to the assumption that OS takes the same form in the subgroup as the overall population; this assumption may not necessarily hold. These analyses suggest the following results:

- PD-L1 TPS <1% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £34,239 (pessimistic) to £34,392 (optimistic) per QALY gained.
- PD-L1 TPS 1-49% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £40,767 (optimistic) to £52,680 (pessimistic) per QALY gained
- PD-L1 TPS ≥50% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £39,193 (optimistic) per QALY gained to dominated (pessimistic). Pembrolizumab monotherapy is ruled out due to strong dominance.

Table 43: ERG's exploratory subgroup analyses - optimistic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS <1% subgroup							
Pembrolizumab combination	3.83	2.03	£64,296	1.98	0.93	£32,126	**£34,392**
Carboplatin+paclitaxel /nab-paclitaxel	1.84	1.10	£32,170	-	-	-	-
PD-L1 TPS 1-49% subgroup							
Pembrolizumab combination	3.60	2.13	£69,348	1.59	0.96	£39,146	**£40,767**
Carboplatin+paclitaxel/ nab-paclitaxel	2.02	1.17	£30,203	-	-	-	-
PD-L1 TPS ≥50% subgroup							
Pembrolizumab combination	4.02	2.11	£64,708	2.02	0.91	£35,519	**£39,193**
Pembrolizumab monotherapy	3.85	2.06	£67,519	-	-	-	**Dominated**
Carboplatin+paclitaxel/ nab-paclitaxel	2.00	1.20	£29,189	-	-	-	-

** undiscounted*
ICER - incremental cost-effectiveness ratio; LYG - life year gained; PD-L1 - programmed death-ligand 1; QALY - quality-adjusted life year

Table 44: ERG's exploratory subgroup analyses - pessimistic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS <1% subgroup							
Pembrolizumab combination	3.29	1.85	£61,898	1.88	0.93	£31,918	**£34,239**
Carboplatin+paclitaxel/ nab-paclitaxel	1.40	0.92	£29,980	-	-	-	-
PD-L1 TPS 1-49% subgroup							
Pembrolizumab combination	3.12	1.91	£67,684	1.03	0.70	£37,023	**£52,680**
Carboplatin+paclitaxel/ nab-paclitaxel	2.09	1.21	£30,661	-	-	-	**-**
PD-L1 TPS ≥50% subgroup							
Carboplatin+paclitaxel/ nab-paclitaxel	4.01	2.03	£38,907	-	-	-	**Dominating**
Pembrolizumab combination	3.72	2.01	£63,425	-	-	-	**Dominated**
Pembrolizumab monotherapy	3.56	1.96	£66,382	-	-	-	**Dominated**

** undiscounted*
ICER - incremental cost-effectiveness ratio; LYG - life year gained; PD-L1 - programmed death-ligand 1; QALY - quality-adjusted life year

5.5 Discussion

The CS[1] includes a systematic review of published economic analyses of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel (pembrolizumab combination therapy) for patients with untreated squamous or non-squamous metastatic NSCLC. The company's review did not identify any relevant economic evaluations, in part due to the specific definition of the intervention in the eligibility criteria for the review.

The CS[1] presents the methods and results of a *de novo* partitioned survival model developed by the company to assess the cost-effectiveness of pembrolizumab combination therapy versus SC chemotherapy for the first-line treatment of patients with squamous metastatic NSCLC (PD-L1 unselected). The CS reports the results of two base cases analyses: "Base Case Analysis 1" compares pembrolizumab combination therapy against carboplatin plus paclitaxel/nab-paclitaxel (the comparator used in KEYNOTE-407[7, 8]), whilst "Base Case Analysis 2" compares pembrolizumab combination therapy against cisplatin/carboplatin in combination with docetaxel, gemcitabine or paclitaxel (the additional comparators included in the company's NMAs[1]). Separate exploratory analyses are also presented for three subgroups defined by PD-L1 TPS (<1%, 1-49% and ≥50%). Within these subgroups, the comparator is carboplatin plus paclitaxel/nab-paclitaxel; an additional indirect comparison is presented against pembrolizumab monotherapy for patients with PD-L1 TPS ≥50%.

Across all analyses, incremental health gains, costs and cost-effectiveness are evaluated over a 30-year time horizon from the perspective of the NHS and PSS. Whilst the CS[1] describes a model in which the partition is defined by the presence/absence of progression, neither the costs nor health outcomes for any treatment strategy are influenced by disease progression. The ERG considers that the company's implemented model is better described as a partitioned survival model based on three health states: (1) receiving first-line treatment; (2) not receiving first-line treatment (including second-line chemotherapy/immunotherapy for some patients), and (3) dead. The model partition impacts only on costs; HRQoL is modelled according to the patient's time to death. The model parameters were informed by analyses of time-to-event data (TTD and OS) collected within KEYNOTE-407, with additional external data from SEER[81] used to model long-term survival. Importantly, the company's model assumes a lifetime treatment effect for the pembrolizumab combination therapy group, despite a maximum treatment duration for pembrolizumab of 2 years. The effectiveness of other SC chemotherapy comparators was estimated from NMAs performed by the company. HRQoL estimates for time-to-death categories were based on EQ-5D assessments within KEYNOTE-407. Resource cost parameters were taken from KEYNOTE-407, standard costing sources,[87, 103] previous TAs, [74, 89-96, 102] additional literature and assumptions.[1]

For Base Case Analysis 1, the probabilistic version of the company's model (using the KM/SEER OS model, including a continued treatment effect for OS) suggests that pembrolizumab combination therapy is expected to generate an additional 1.68 QALYs at an additional cost of £48,387 per patient; the corresponding ICER is £28,852 per QALY gained. The deterministic version of the company's model produces a very similar ICER of £28,672 per QALY gained. The probability that pembrolizumab combination therapy produces more net benefit than carboplatin plus paclitaxel/nab-paclitaxel at WTP thresholds (λ) of £30,000 and £50,000 per QALY gained is 0.55 and 0.94, respectively.

For Base Case Analysis 2, a fully incremental analysis of pembrolizumab combination therapy versus all treatment comparators from KEYNOTE-407 and the company's NMAs suggest that: cisplatin/carboplatin plus docetaxel is the least effective option; carboplatin plus paclitaxel/nab-paclitaxel (the KEYNOTE-407 comparator regimen) is dominated by cisplatin/carboplatin plus paclitaxel; the ICERs for cisplatin/carboplatin plus gemcitabine and cisplatin/carboplatin plus paclitaxel versus their next best non-dominated comparators are less than £9,000 per QALY gained, and the ICER for pembrolizumab combination therapy versus platinum plus gemcitabine is approximately £63,661 per QALY gained. The ERG identified errors in the model which render these results unreliable; the correction of these errors reduces the company's ICER for pembrolizumab combination therapy versus platinum plus gemcitabine to £51,240 per QALY gained. Probabilistic results for this analysis were not reported in the CS and could not be easily generated using the company's model.

The company's PD-L1 subgroup analyses suggest ICERs for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel which are in the range £25,849 to £32,174 per QALY gained. Within the PD-L1 TPS ≥50% subgroup, the company's model suggests that pembrolizumab combination therapy is ruled out of the analysis due to extended dominance. However, the ERG identified errors in this analysis; the correction of these errors leads to a situation whereby pembrolizumab monotherapy is ruled out due to strong dominance.

The ERG critically appraised the company's health economic analyses and double-programmed the deterministic version of the company's model (for Base Case Analyses 1 and 2 and for the PD-L1 TPS subgroup analyses). The ERG's critical appraisal identified a number of issues relating to the company's model and the evidence used to inform its parameters. The most pertinent of these include: (i) the identification of model errors; (ii) concerns relating to the company's NMAs, in particular, the absence of second-line immunotherapy from the trials of SC chemotherapy comparator regimens; (iii) uncertainty surrounding long-term extrapolation; (iv) the potentially optimistic assumption of a lifetime OS treatment effect for pembrolizumab combination therapy; (v) the inclusion of an implicit assumption of cure within the model, and (vi) concerns regarding the company's approach to modelling HRQoL.

The ERG notes that the OS data from KEYNOTE-407 are immature and alternative assumptions regarding long-term OS benefits have the propensity to increase the ICER substantially.

The ERG undertook six sets of exploratory analyses using the deterministic version of the company's model. The ERG's preferred model includes the following amendments: (i) the correction of model errors; (ii) the inclusion of health state utilities defined according to the presence/absence of disease progression (together with the use of PFS data applied as the model partition); (iii) the use of disease management costs defined according to the presence/absence of disease progression; (iv) increased costs associated with second-line immunotherapy, and (v) the use of clinicians' preferred OS models. The ERG's preferred analyses combine all of these amendments and are presented across two separate scenarios: (i) an optimistic scenario, and (ii) a pessimistic scenario. The ERG's preferred optimistic scenario suggests an ICER for pembrolizumab combination therapy versus SC chemotherapy of £35,981 per QALY gained, whilst the ERG's preferred pessimistic scenario suggests a higher ICER of £49,473 per QALY gained. Additional sensitivity analyses using the full range of ERG-fitted standard parametric models and natural cubic spline models lead to ICERs ranging from £35,981 to £274,028 per QALY gained. The ERG's exploratory subgroup analyses, which are based on the same parametric OS models as those applied in the overall population (PD-L1 unselected), suggest the following results:

- PD-L1 TPS <1% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £34,239 (pessimistic) to £34,392 (optimistic) per QALY gained.
- PD-L1 TPS 1-49% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £40,767 (optimistic) to £52,680 (pessimistic) per QALY gained
- PD-L1 TPS ≥50% - the ICER for pembrolizumab combination therapy versus SC chemotherapy ranges from £39,193 (optimistic) per QALY gained to dominated (pessimistic). Pembrolizumab monotherapy is ruled out due to strong dominance.

The ERG notes that additional data collection in KEYNOTE-407 may resolve some of the uncertainty surrounding expected outcomes, both within the overall metastatic squamous NSCLC population and within specific PD-L1 TPS subgroups.

6 END OF LIFE

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

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

The ERG notes that owing to the short follow-up in IA2 of the KEYNOTE-407 trial,[7, 8] and the potential benefits of second-line immunotherapy in the SC chemotherapy group, the expected survival duration for patients receiving pembrolizumab combination therapy and standard care is subject to considerable uncertainty. At the time of IA2 in KEYNOTE-407, median OS was 15.9 months in the pembrolizumab combination therapy group and 11.3 months in the carboplatin plus paclitaxel/nab-paclitaxel group (difference=4.6 months). Table 45 summarises the undiscounted mean survival for carboplatin plus paclitaxel/nab-paclitaxel, the incremental survival gain for pembrolizumab combination therapy and the ICER based on the company's corrected base case (ERG exploratory analysis 1), the ERG's preferred optimistic and pessimistic analyses (ERG exploratory analyses 6a and 6b), and the full range of parametric OS models fitted by the ERG (ERG sensitivity analysis 4). The table also indicates whether both of NICE's EoL criteria are met for each OS model scenario.

The ERG-corrected company's base case analysis and the ERG's preferred optimistic analysis suggest that pembrolizumab combination therapy meets NICE's EoL criteria (standard care OS = 1.97 years; life extension = 1.98 to 3.12 years; ICER <£36,000 per QALY gained). Within the ERG's preferred pessimistic analysis, pembrolizumab combination therapy meets the life extension criterion, but does not meet the 24-month expected survival criterion (standard care OS = 2.17 years; life extension = 1.06 years; ICER = £49,473 per QALY gained). Across the full range of ERG-fitted OS models, the EoL criteria are met in the majority of scenarios, however the ICER for pembrolizumab combination therapy remains above £50,000 per QALY gained across all of these scenarios.

Table 45: Undiscounted survival for comparator groups and incremental survival gain

OS model	Comparator group outcomes			Incremental – pembrolizumab combination vs. SC chemotherapy		EoL criteria met?
	Mean OS (undiscounted)	1-year OS	2-year OS	Incremental OS (years)	ICER*	
Company's original model (company's KM/SEER model)	1.97	48%	22%	3.09	**£28,693**	**yes**
ERG optimistic scenario (company's KM/log logistic model)	1.97	48%	22%	1.98	**£35,981**	**yes**
ERG pessimistic scenario (ERG's log logistic model)	2.17	50%	27%	1.06	**£49,473**	**no**
Generalised gamma (ERG-fitted)	1.17	49%	17%	0.14	**£233,327**	**no**
Gamma (ERG-fitted)	1.30	50%	21%	0.58	**£76,057**	**yes**
Log normal (ERG-fitted)	2.58	52%	33%	1.49	**£42,193**	**no**
Log logistic (ERG-fitted)	2.17	50%	27%	1.06	**£49,473**	**no**
Weibull (ERG-fitted)	1.24	49%	19%	0.51	**£84,320**	**yes**
Gompertz (ERG-fitted)	1.09	50%	13%	0.26	**£144,595**	**yes**
Exponential (ERG-fitted)	1.50	51%	26%	0.81	**£60,302**	**yes**
Spline k=1,scale=hazard (ERG-fitted)	1.18	49%	17%	0.46	**£91,995**	**yes**
Spline k=2,scale=hazard (ERG-fitted)	1.24	49%	19%	0.27	**£135,956**	**yes**
Spline k=3,scale=hazard (ERG-fitted)	1.47	48%	24%	0.06	**£274,028**	**no**
Spline k=1,scale=normal (ERG-fitted)	1.54	49%	23%	1.03	**£51,611**	**yes**
Spline k=2,scale=normal (ERG-fitted)	1.37	49%	20%	0.56	**£78,446**	**yes**
Spline k=3,scale=normal (ERG-fitted)	1.75	48%	25%	0.26	**£116,905**	**yes**
Spline k=1,scale=odds (ERG-fitted)	1.73	49%	23%	0.94	**£54,645**	**yes**
Spline k=2,scale=odds (ERG-fitted)	1.60	48%	21%	0.55	**£78,200**	**yes**
Spline k=3,scale=odds (ERG-fitted)	2.08	48%	26%	0.13	**£130,059**	**no**

7 OVERALL CONCLUSIONS

The clinical evidence regarding the efficacy of pembrolizumab combination therapy for untreated metastatic squamous NSCLC is broadly reliable and relevant to the decision problem. The main source of evidence in the CS[1] is from a single high-quality RCT (KEYNOTE-407[7, 8]). This trial reported that pembrolizumab combination therapy was statistically superior to SC chemotherapy for OS, PFS, and DoR outcomes. Reporting of safety data in this trial was limited to 30 days for AEs and 90 days for SAEs after the last dose of study treatment. The ERG notes that stopping data collection after these cut-off dates will limit the validity of the evidence relating to the toxicity profile for patients undergoing immunotherapy in combination with SC chemotherapy. Data on baseline PD-L1 expression for patients who switched from the SC chemotherapy to immunotherapy from the final analysis of KEYNOTE-407 would be informative. There remains uncertainty surrounding whether pembrolizumab should be given as first-line combination therapy or as monotherapy for patients with PD-L1 strong expression.

The exploratory analyses undertaken by the ERG led to an ICER for pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel of £35,981 per QALY gained under optimistic OS assumptions, and an ICER of £49,473 per QALY gained under pessimistic OS assumptions. These estimates are higher than the company's original base case estimate of £28,852 per QALY gained (the company's probabilistic ICER for this comparison). Given the limitations of the available evidence from IA2 of KEYNOTE-407,[7, 8] the ERG notes that there is considerable uncertainty surrounding the expected OS outcomes for patients receiving pembrolizumab combination therapy and for those receiving SC chemotherapy (in part, due to the use of second-line immunotherapy as part of the SC pathway in England). Additional sensitivity analyses using alternative OS functions within the ERG's preferred model produced ICERs which range from £35,981 to £274,028 per QALY gained; several of these estimates are higher than the ERG's pessimistic scenario. The ERG's exploratory subgroup analyses suggest optimistic ICERs which range from £34,392 to £39,193 per QALY gained across all PD-L1 subgroups, and pessimistic ICERs which range from £34,239 to dominated across the PD-L1 subgroups.

Given the uncertainty in the OS estimates based on IA2 of KEYNOTE-407,[7, 8] it is unclear whether pembrolizumab combination therapy meets NICE's EoL criteria.

7.1 Implications for research

The ERG notes that additional data collection in KEYNOTE-407 may resolve some of the uncertainty surrounding expected outcomes in the overall squamous NSCLC population and within specific PD-L1 TPS subgroups. Evidence regarding the safety of pembrolizumab combination therapy is immature. In view of the delayed onset and prolonged duration of IRAEs, consideration of extension studies and real-

world data will be key to providing externally valid documentation of the safety of pembrolizumab combination therapy in the proposed indication.

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9 APPENDICES

Appendix 1: AIC and BIC statistics for company's piecewise parametric curve-fitting for OS

Table 46: AIC and BIC statistics for company's piecewise parametric curve-fitting for OS*

Week 9 cut-point				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Week 19 cut-point				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Week 29 cut-point				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; SC - standard care
** Best fitting models (lowest AIC/BIC) presented in bold*

Appendix 2: Time-to-event models and additional parameters used in company's subgroup analyses

Table 47: AIC and BIC statistics for company's piecewise parametric curve-fitting for OS, cutoff point 19 weeks (adapted from the company's model)

PD-L1<1%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 1-49%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1≥50%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; N/A – not available; PD-L1 - programmed death-ligand 1; SC - standard care

** Best fitting models (lowest AIC/BIC) presented in bold*

Figure 21: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, pembrolizumab combination therapy group in KEYNOTE-407,[7, 8] PD-L1 TPS≥50%

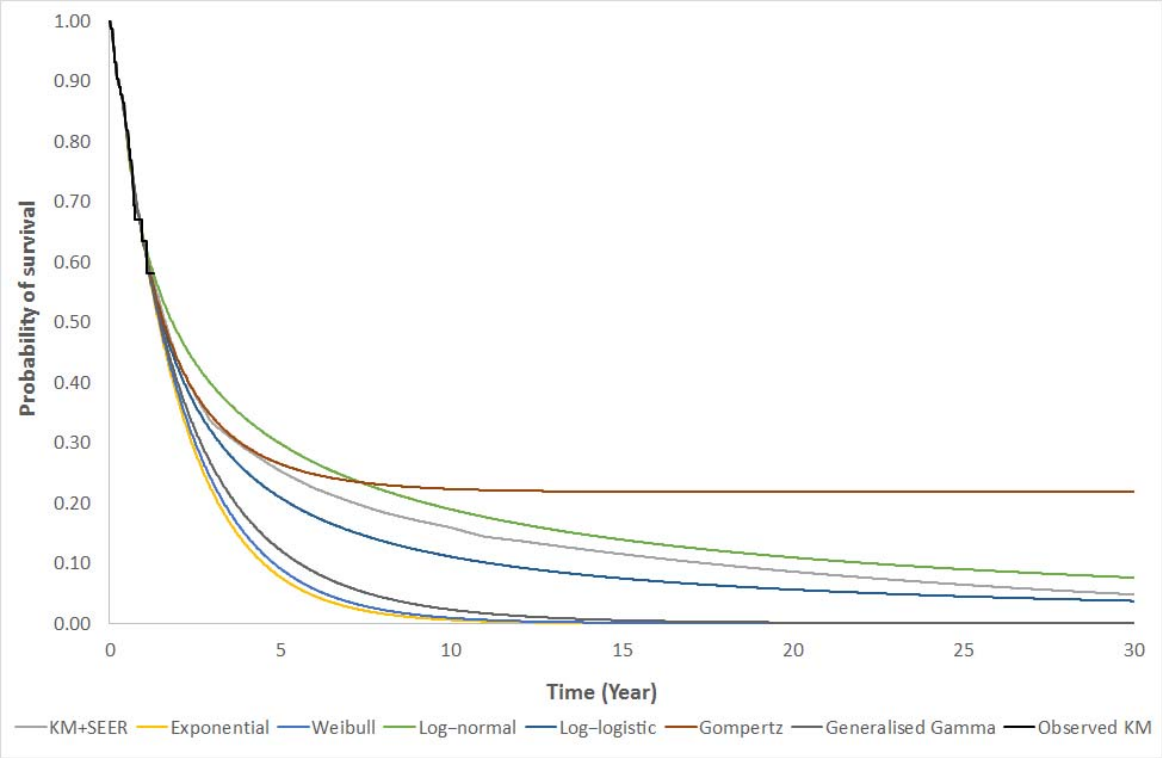


Figure 22: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, pembrolizumab combination therapy group in KEYNOTE-407,[7, 8] PD-L1 TPS 1-49%

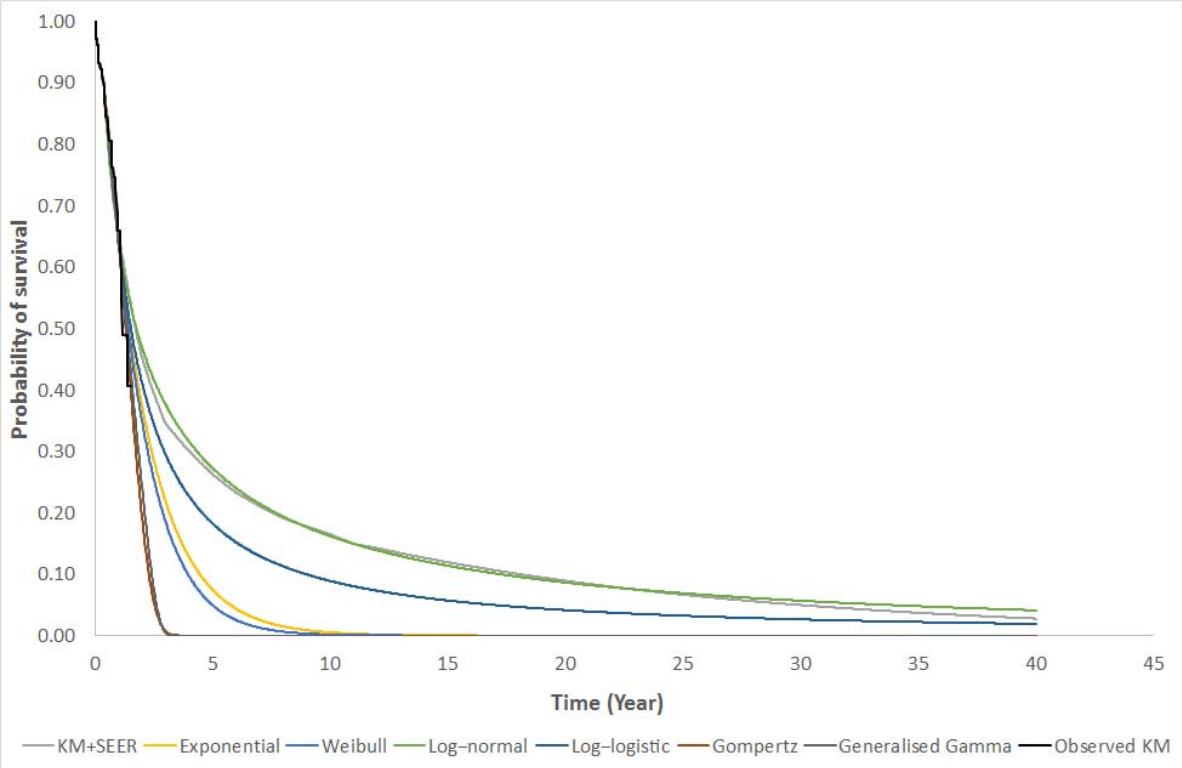


Figure 23: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, pembrolizumab combination therapy group in KEYNOTE-407,[7, 8] PD-L1 TPS <1%

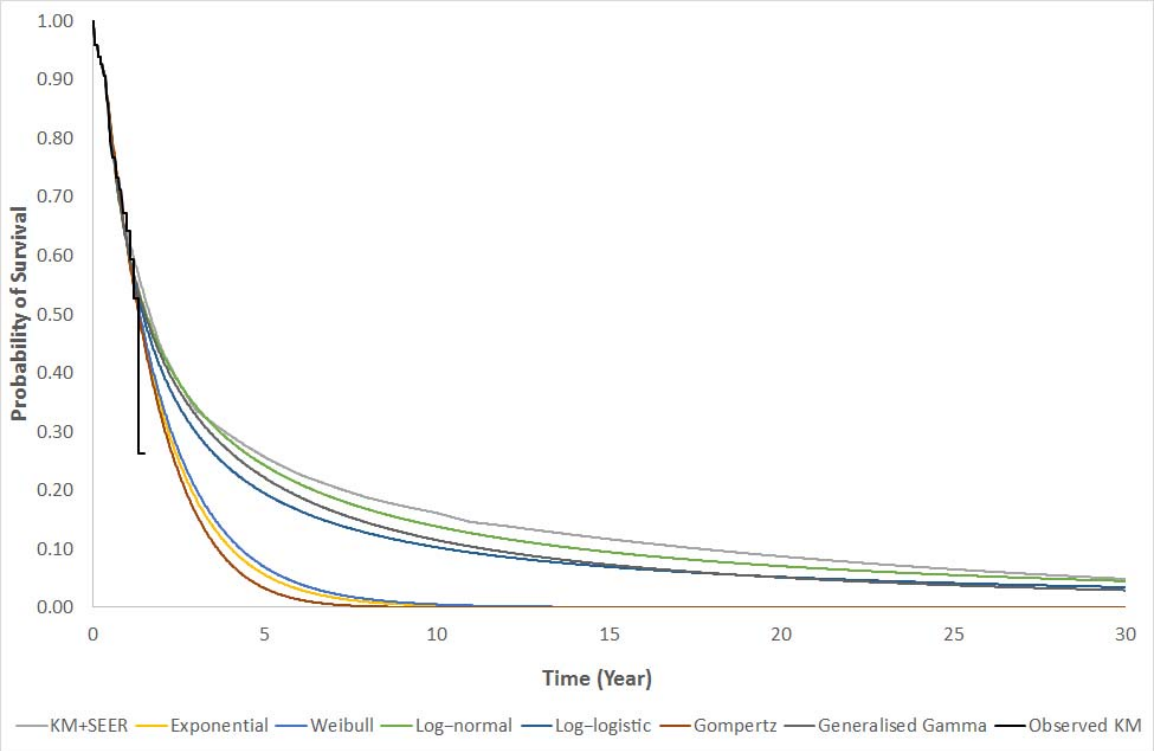


Figure 24: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, SC chemotherapy group in KEYNOTE-407, [7, 8] PD-L1 TPS≥50%

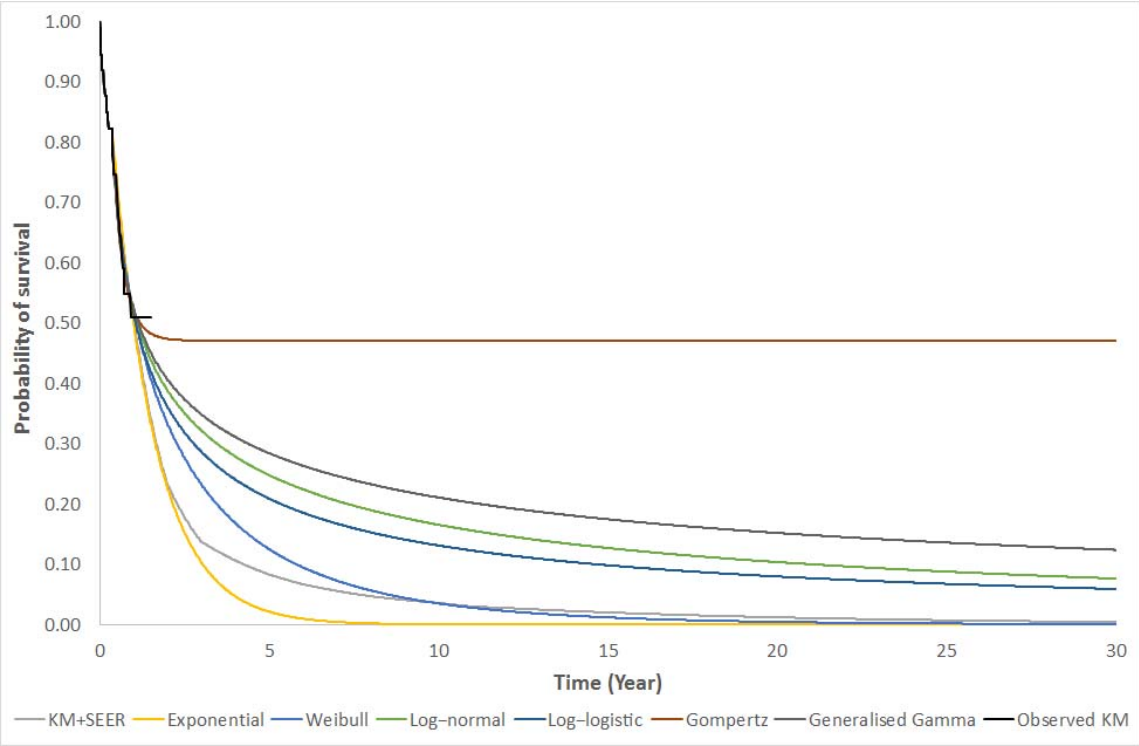


Figure 25: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, SC chemotherapy group in KEYNOTE-407,[7, 8] PD-L1 TPS 1-49%

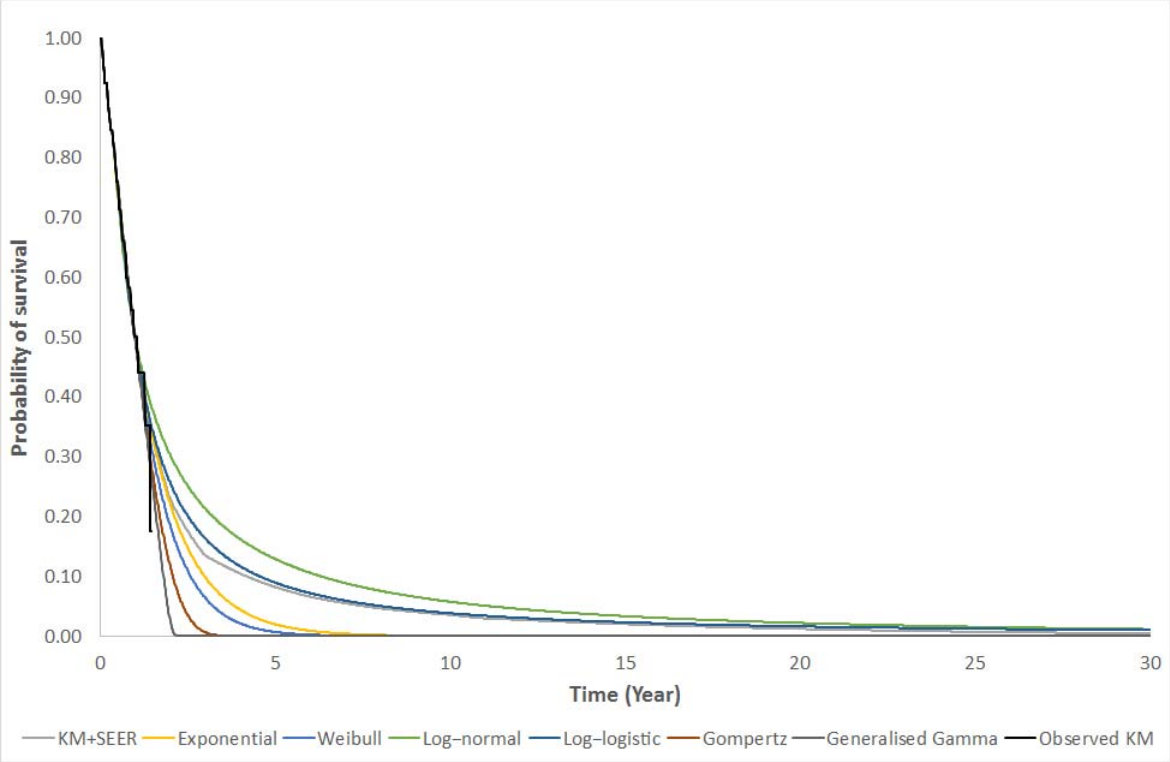


Figure 26: Modelled OS functions estimated using Kaplan-Meier plus SEER and piecewise parametric curve-fitting approaches, SC chemotherapy group in KEYNOTE-407, [7, 8] PD-L1 TPS<1%

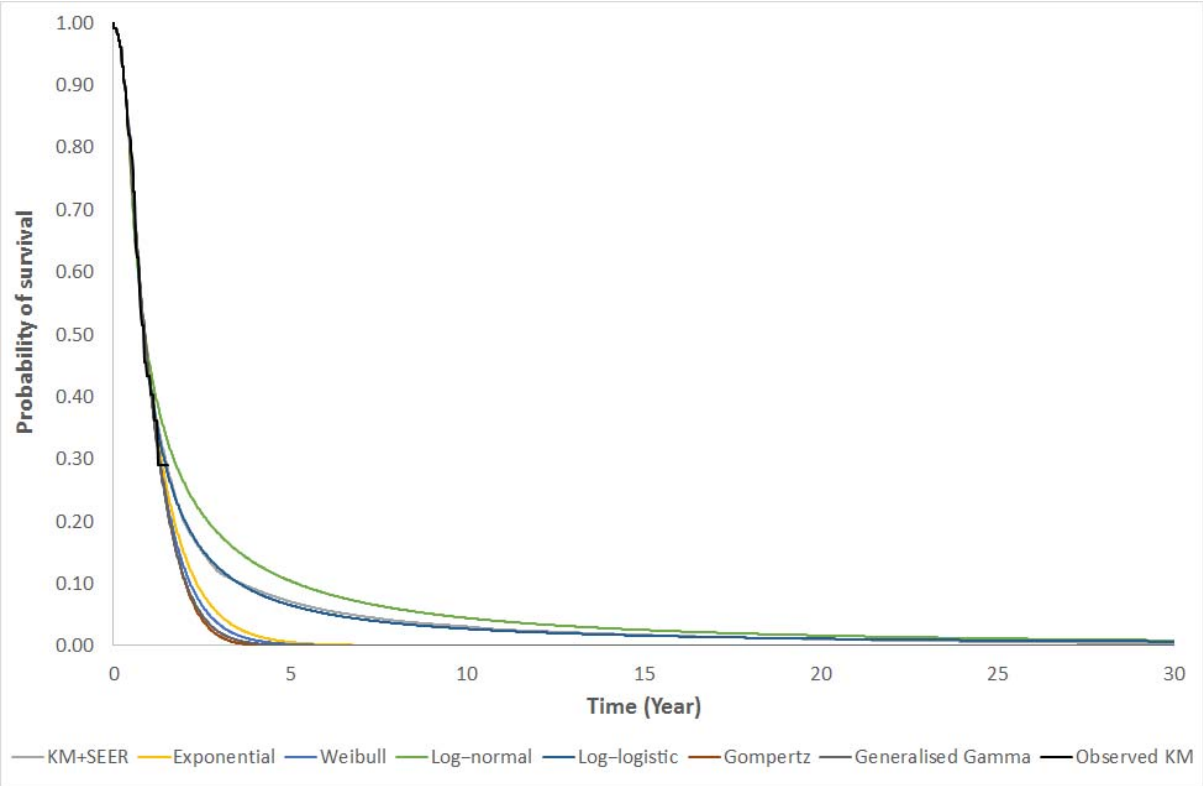


Table 48: AIC and BIC statistics for company's piecewise parametric curve-fitting for PFS, cutoff point 26 weeks (adapted from the company's model)

PD-L1<1%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential				
Weibull				
Log normal				
Log logistic				
Gompertz				
Generalised gamma				
PD-L1 1-49%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential				
Weibull				
Log normal				
Log logistic				
Gompertz				
Generalised gamma				
PD-L1≥50%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential				
Weibull				
Log normal				
Log logistic				
Gompertz				
Generalised gamma				

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; N/A – not available; PD-L1 - programmed death-ligand 1; SC - standard care

** Best fitting models (lowest AIC/BIC) presented in bold*

Figure 27: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, pembrolizumab combination therapy group, PD-L1 TPS≥50%

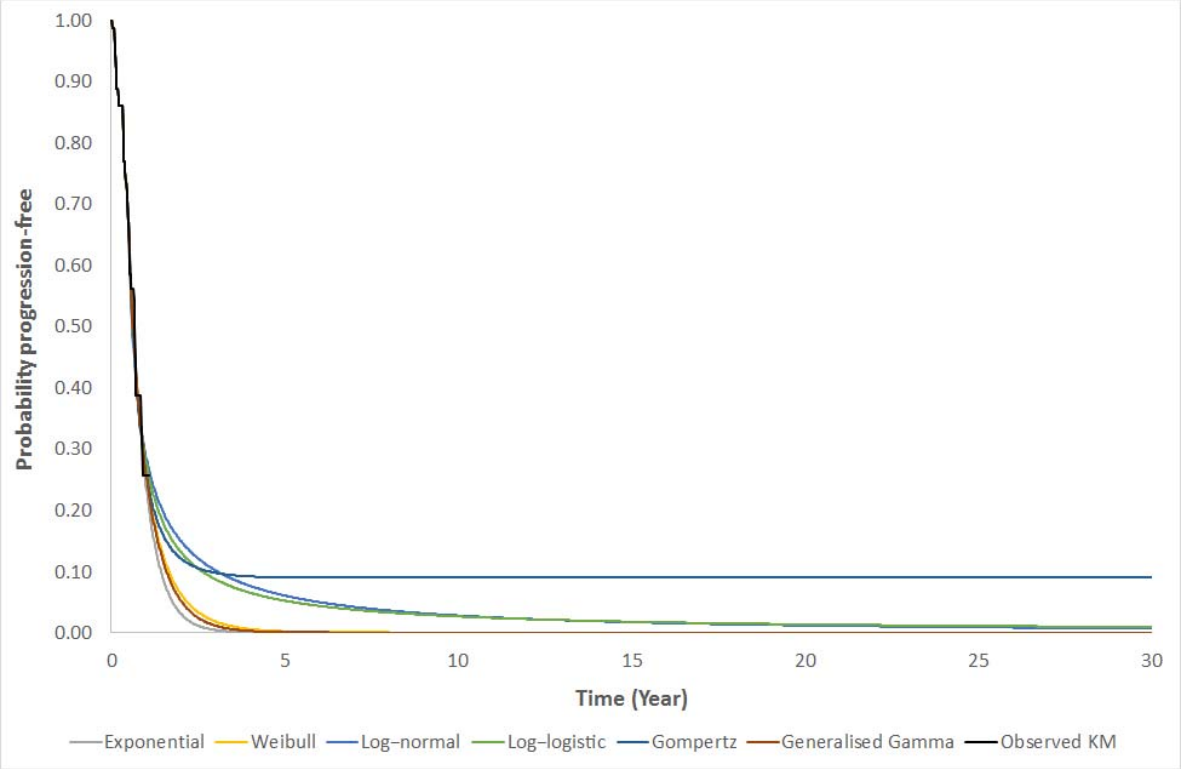


Figure 28: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, pembrolizumab combination therapy group, PD-L1 TPS 1-49%

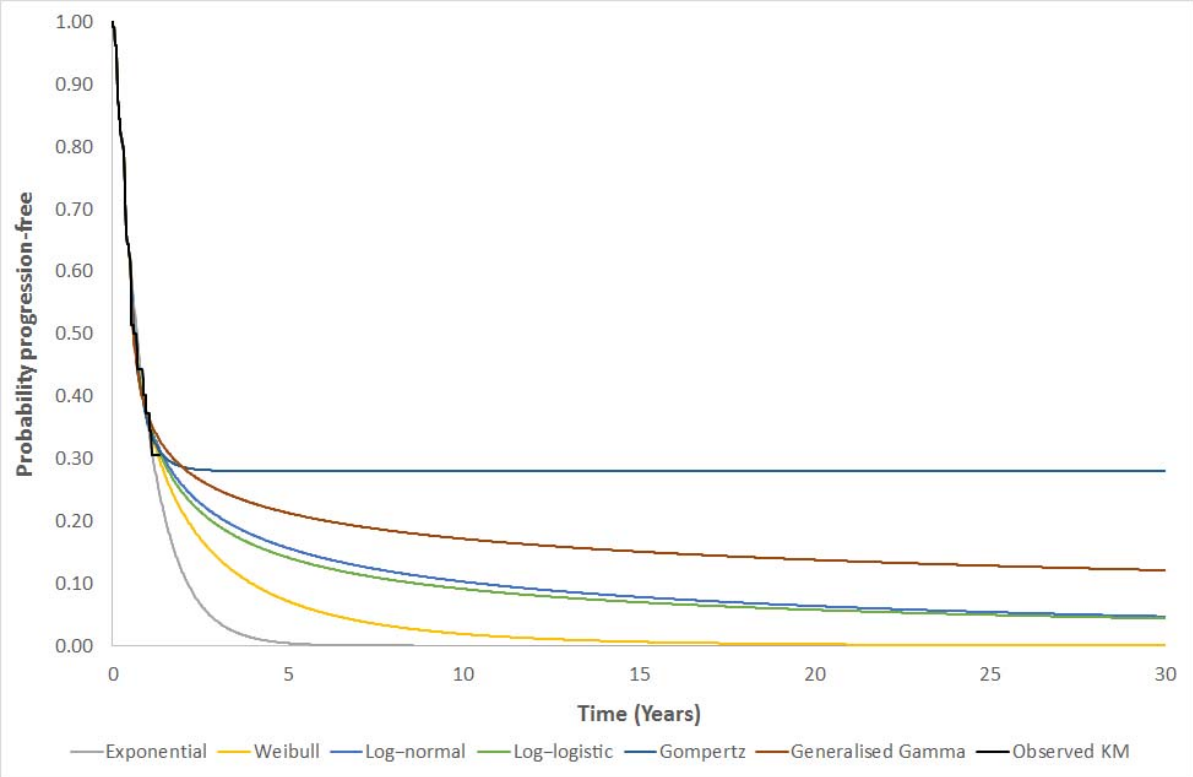


Figure 29: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, pembrolizumab combination therapy group, PD-L1 TPS<1%

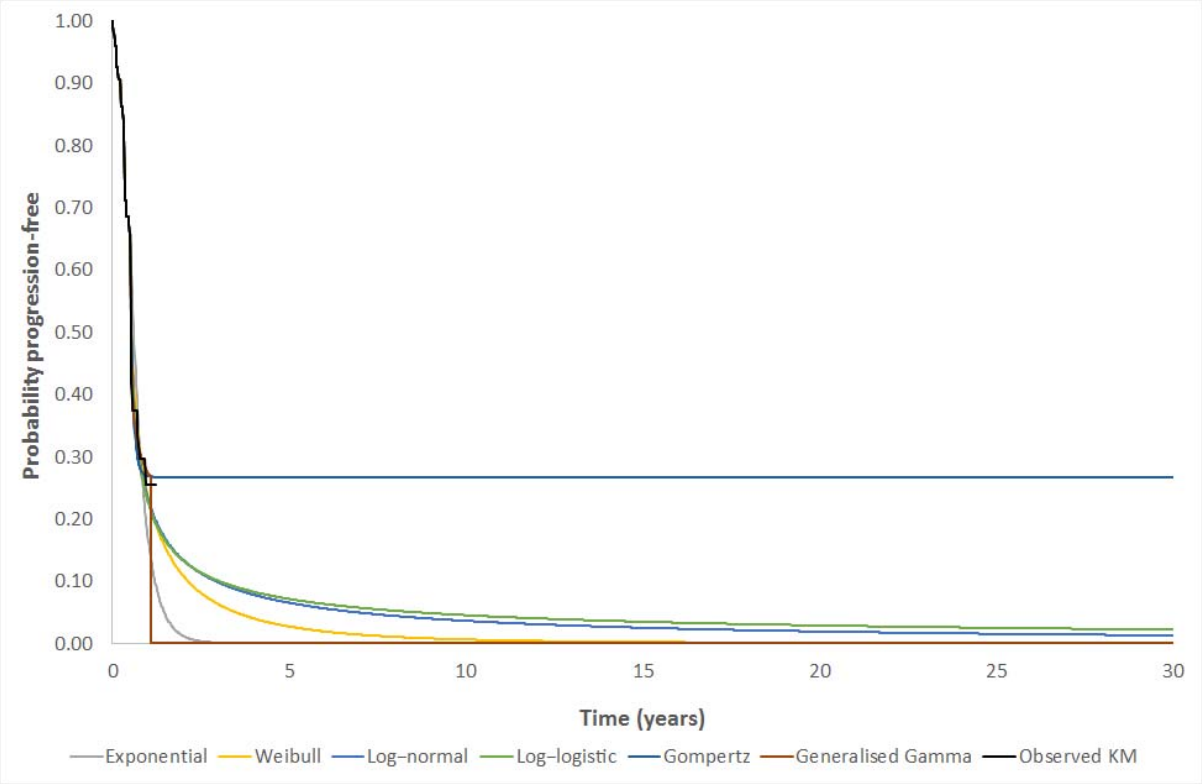


Figure 30: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, SC chemotherapy group, PD-L1 TPS≥50%

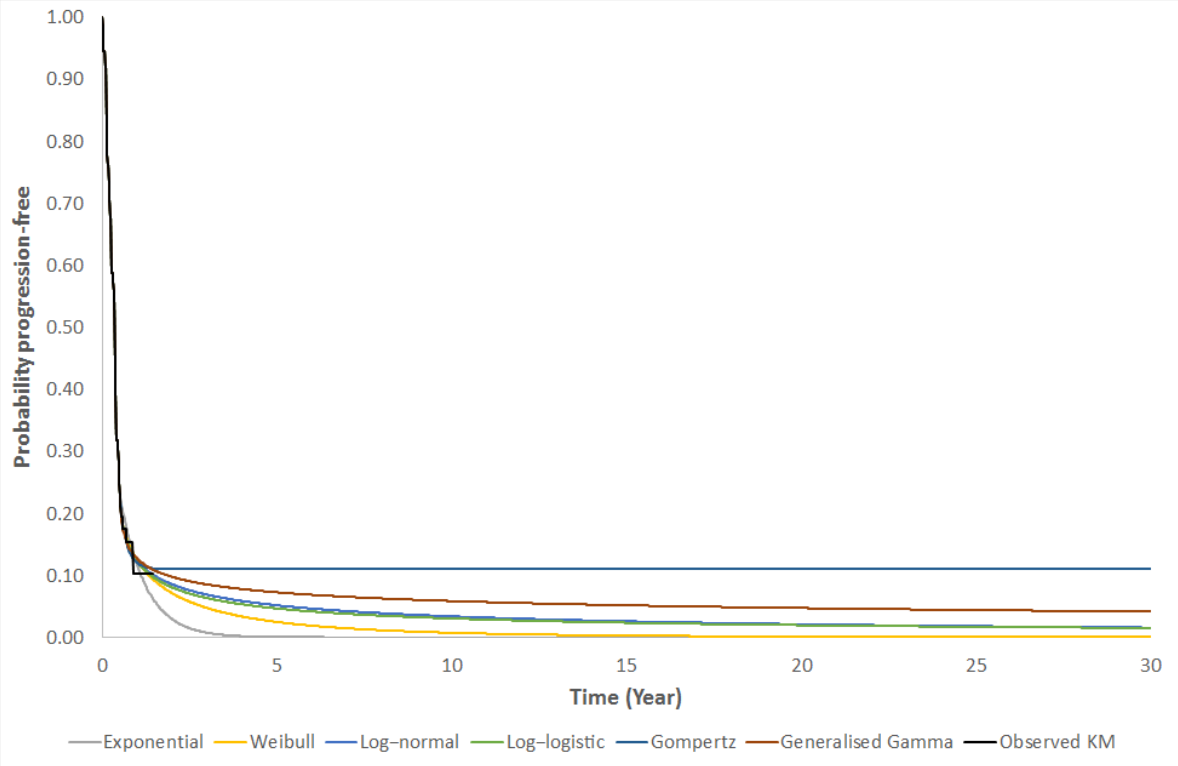


Figure 31: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, SC chemotherapy group, PD-L1 TPS 1-49%

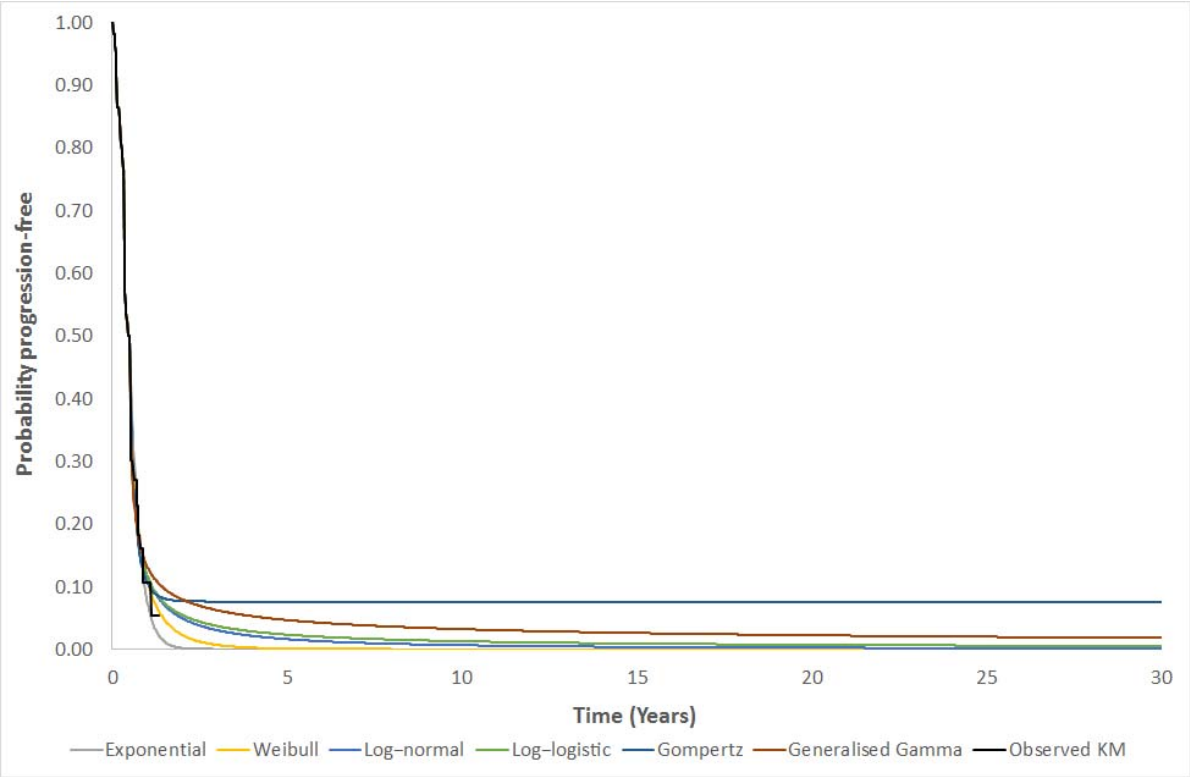


Figure 32: Plots of cumulative PFS from company's piecewise parametric curve-fitting for PFS, SC chemotherapy group, PD-L1 TPS<1%

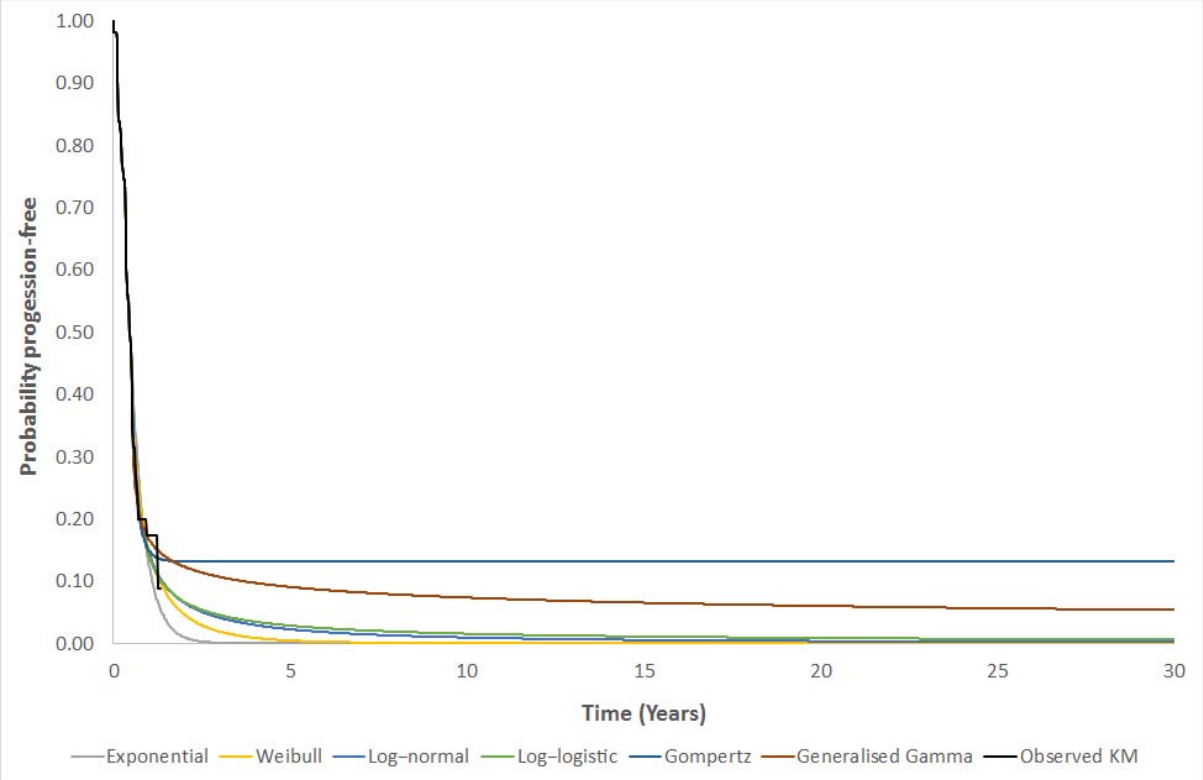


Table 49: AIC and BIC statistics for company's parametric curve-fitting for TTD within the PD-L1 subgroups (adapted from the company's model)

PD-L1 <1%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	N/A	N/A
Weibull	[redacted]	[redacted]	N/A	N/A
Log normal	[redacted]	[redacted]	N/A	N/A
Log logistic	[redacted]	[redacted]	N/A	N/A
Gompertz	[redacted]	[redacted]	N/A	N/A
Generalised gamma	[redacted]	[redacted]	N/A	N/A
PD-L1 1-49%				
Model	**Pembrolizumab combination**		**SC chemotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	N/A	N/A
Weibull	[redacted]	[redacted]	N/A	N/A
Log normal	[redacted]	[redacted]	N/A	N/A
Log logistic	[redacted]	[redacted]	N/A	N/A
Gompertz	[redacted]	[redacted]	N/A	N/A
Generalised gamma	[redacted]	[redacted]	N/A	N/A
PD-L1 ≥50%				
Model	**Pembrolizumab combination**		**Pembrolizumab monotherapy**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	N/A	N/A
Weibull	[redacted]	[redacted]	N/A	N/A
Log normal	[redacted]	[redacted]	N/A	N/A
Log logistic	[redacted]	[redacted]	N/A	N/A
Gompertz	[redacted]	[redacted]	N/A	N/A
Generalised gamma	[redacted]	[redacted]	N/A	N/A

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; N/A - not available; PD-L1 - programmed death-ligand 1; SC - standard care

** Best fitting models (lowest AIC/BIC) presented in bold*

Figure 33: TTD modelled curves from company's parametric curve-fitting, pembrolizumab combination therapy, PD-L1 TPS<1% subgroup

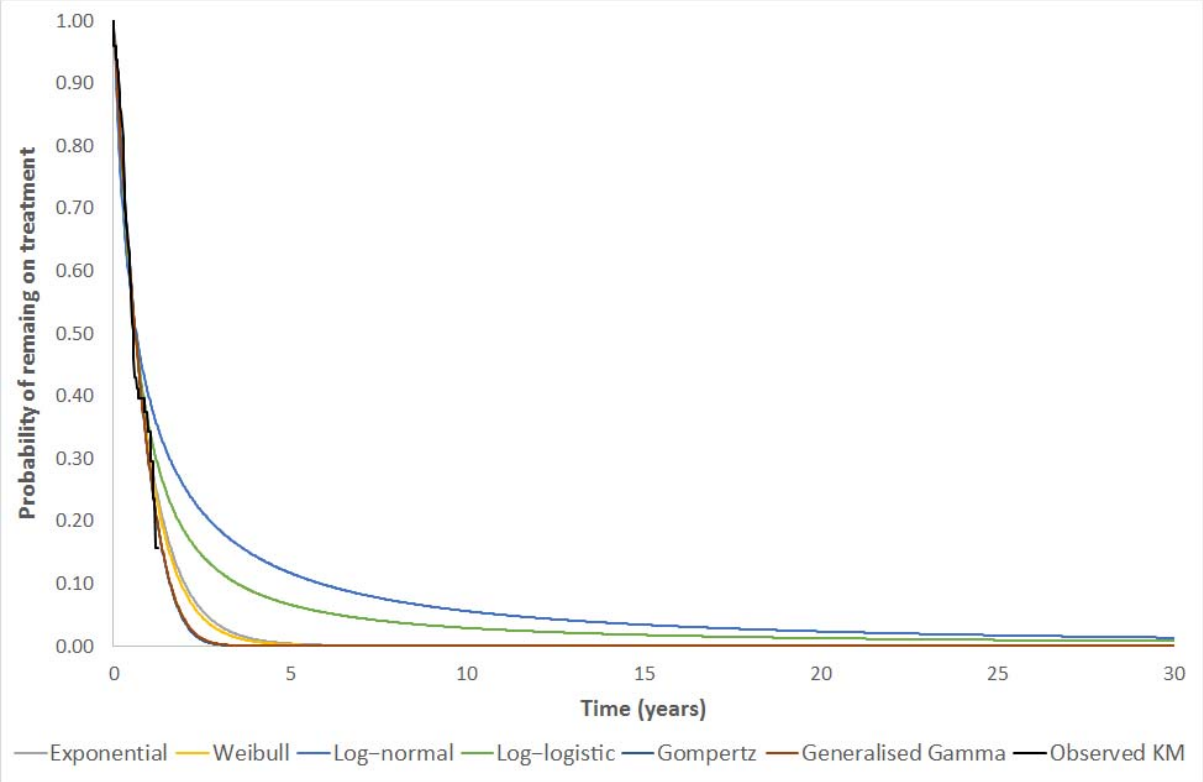


Figure 34: TTD modelled curves from company's parametric curve-fitting, pembrolizumab combination therapy, PD-L1 TPS 1-49% subgroup

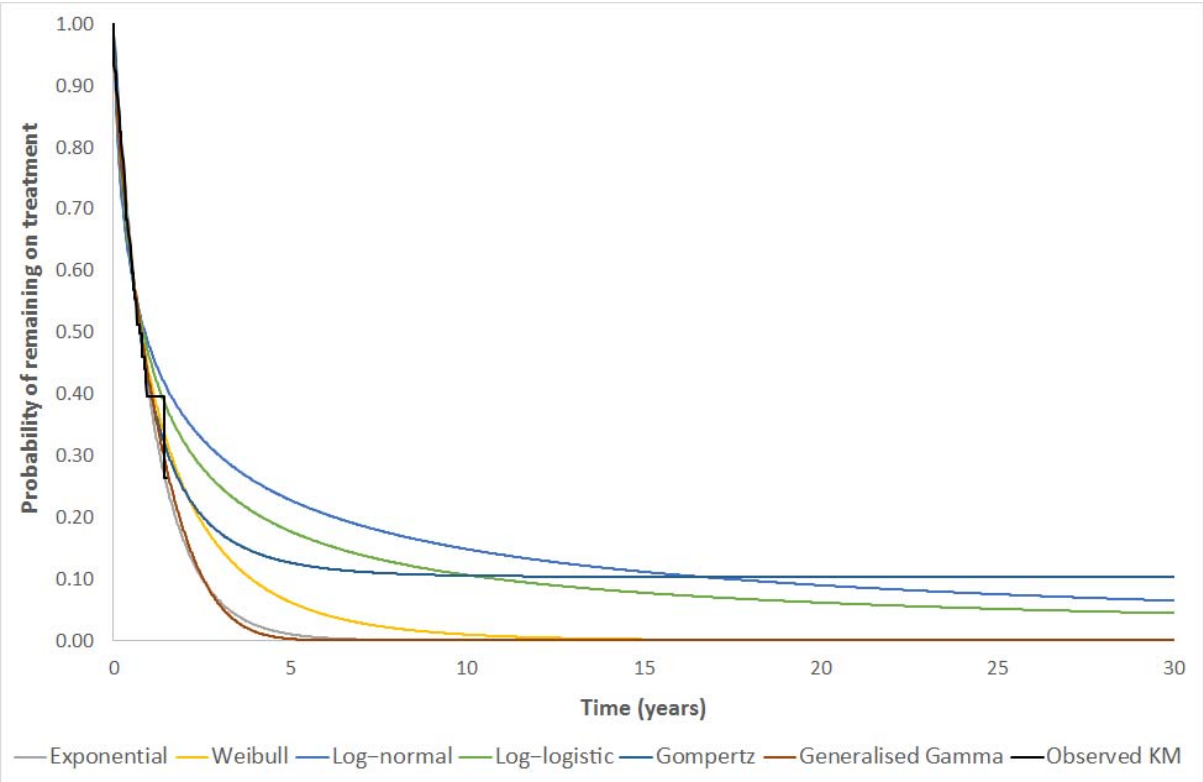


Figure 35: TTD modelled curves from company's parametric curve-fitting, pembrolizumab combination therapy, PD-L1 TPS ≥50% subgroup

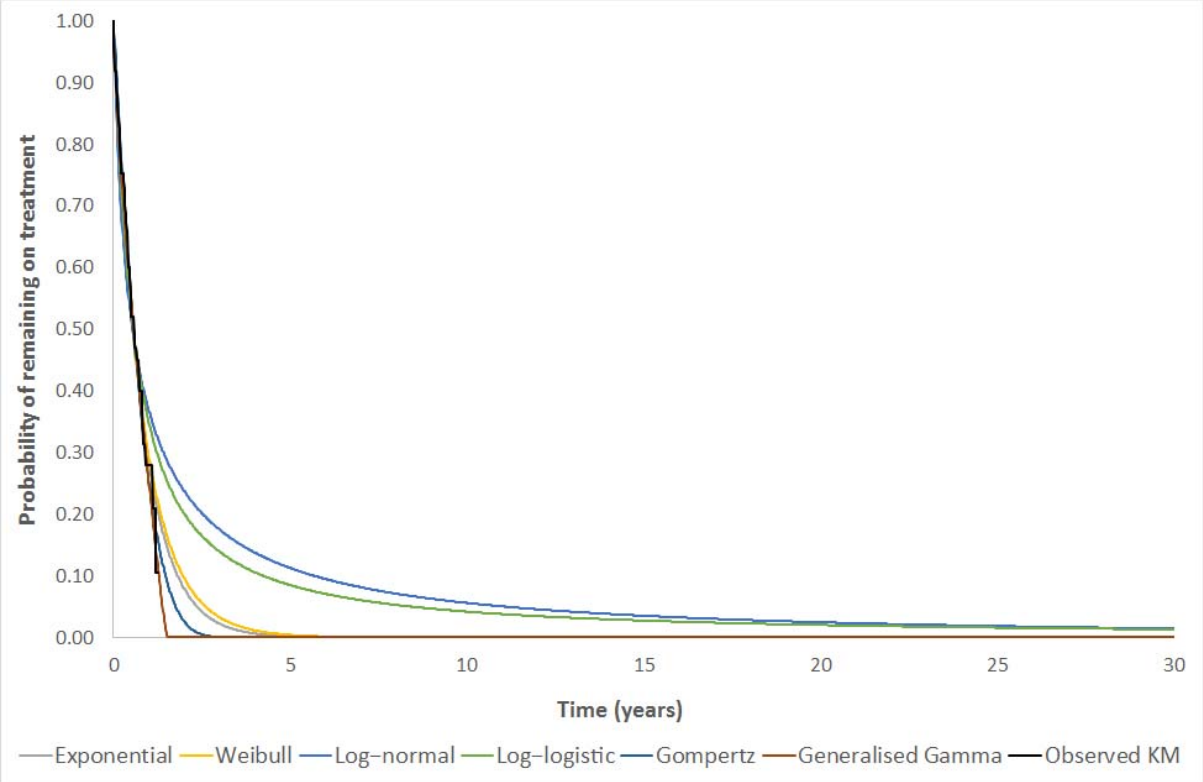


Figure 36: TTD functions for pembrolizumab combination therapy, SC chemotherapy and pembrolizumab monotherapy, PD-L1 TPS ≥50% subgroup

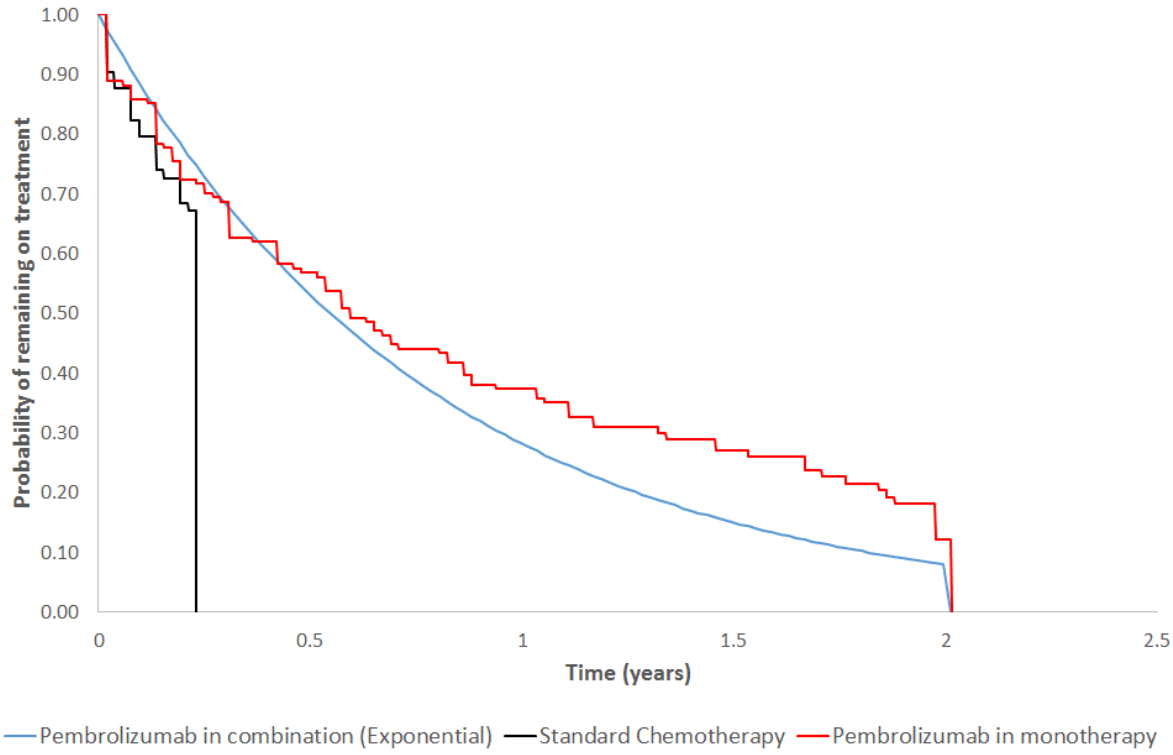


Figure 37: TTD functions for pembrolizumab combination therapy and SC chemotherapy, PD-L1 TPS 1-49% subgroup

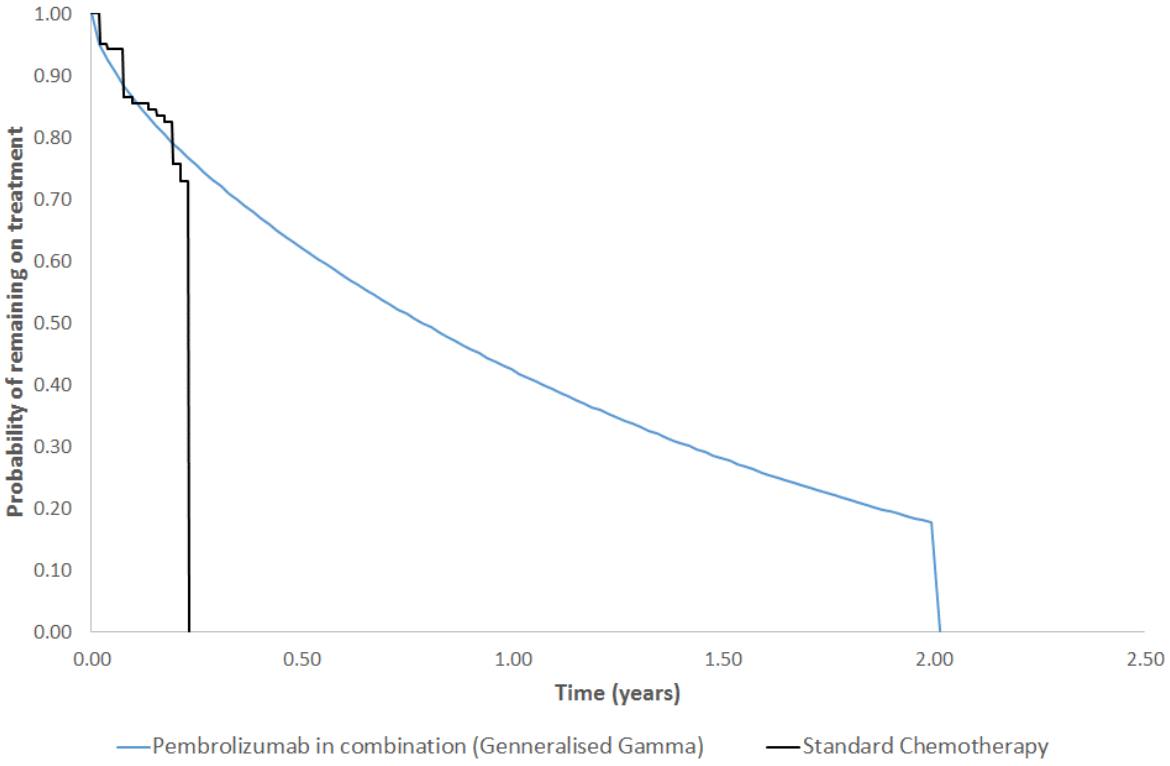


Figure 38: TTD functions for pembrolizumab combination therapy and SC chemotherapy, PD-L1 TPS <1% subgroup

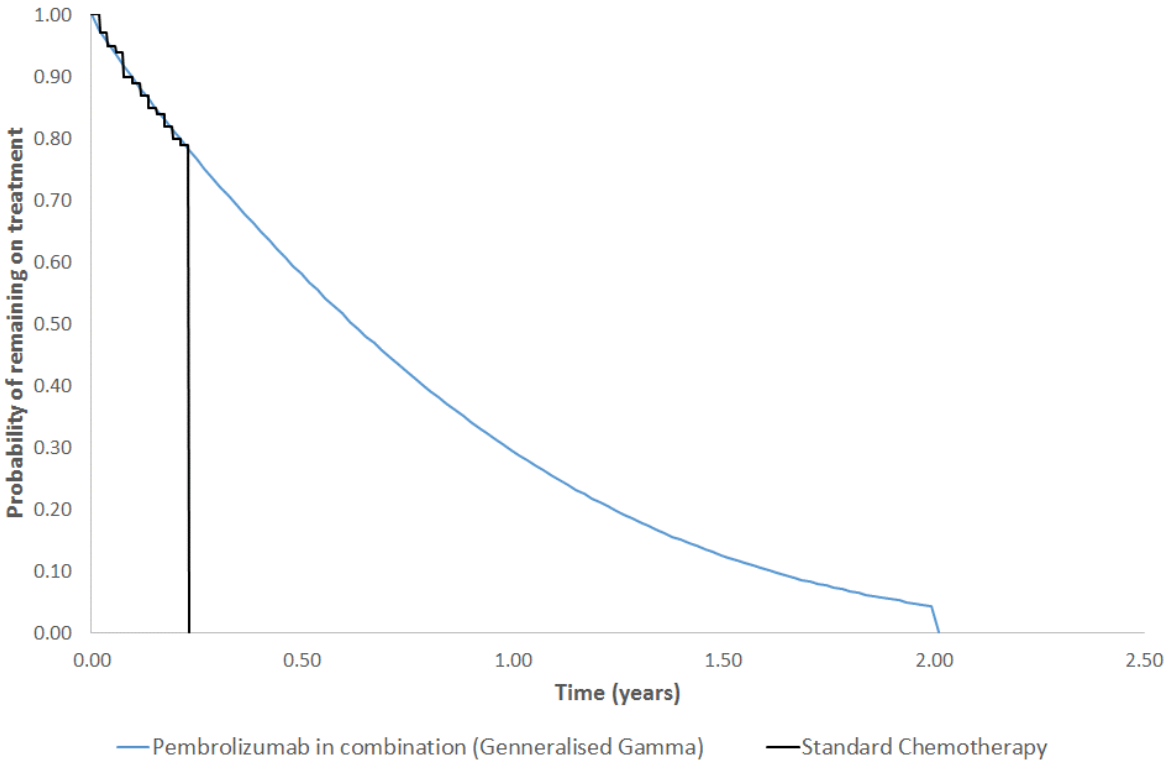


Table 50: Incidence rates and unit costs for Grade 3-5 AEs used in the model for subgroup analyses

Adverse Event	Pembrolizumab combination (all subgroups)	Chemotherapy (all subgroups)	Pembrolizumab monotherapy (PD-L1≥50%)	Unit costs	Source
Nausea	[redacted]	[redacted]	[redacted]	£998.38	Brown *et al*[88]
Anaemia	[redacted]	[redacted]	[redacted]	£2,692.61	TA428[89]
Fatigue	[redacted]	[redacted]	[redacted]	£2,855.25	Brown *et al*[88]
Decreased appetite	[redacted]	[redacted]	[redacted]	£0.00	TA428[89]
Constipation	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Diarrhoea (grade 2)	[redacted]	[redacted]	[redacted]	£456.66	TA428[89]
Diarrhoea (grade 3-4)	[redacted]	[redacted]	[redacted]	£998.38	Brown *et al*[88]
Dyspnoea	[redacted]	[redacted]	[redacted]	£588.98	TA403[90]
Vomiting	[redacted]	[redacted]	[redacted]	£813.47	TA192[91]
Back pain	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Arthralgia	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Neutropenia	[redacted]	[redacted]	[redacted]	£120.99	Brown *et al*[88]
Oedema peripheral	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Blood creatinine increased	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	£637.03	TA347[92]
Dizziness	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Rash	[redacted]	[redacted]	[redacted]	£127.21	Brown *et al*[88]
Asthenia	[redacted]	[redacted]	[redacted]	£2,855.25	Brown *et al*[88]
Chest pain	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Stomatitis	[redacted]	[redacted]	[redacted]	£0.00	TA428[89]
Hyponatraemia	[redacted]	[redacted]	[redacted]	£0.00	TA357[93]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	£782.31	TA406[94]
Neuropathy Peripheral	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Abdominal pain	[redacted]	[redacted]	[redacted]	£0.00	TA395[95]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	£364.64	TA347[92]
Peripheral Sensory Neuropathy	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Pyrexia	[redacted]	[redacted]	[redacted]	£261.00	NHS Reference Costs 16/17[87§]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Pneumonia	[redacted]	[redacted]	[redacted]	£3,102.84	TA411[74]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	£577.66	TA428[89]
Haemoptysis	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Pain in extremity	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Cough	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Myalgia	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Pruritis	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	£171.14	Assume the same as lower respiratory tract infection[¤]
Leukopenia	[redacted]	[redacted]	[redacted]	£0.00	TA406[94]
Epistaxis	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Neutrophil Count Decreased	[redacted]	[redacted]	[redacted]	£577.66	TA428[89]
Pneumonitis	[redacted]	[redacted]	[redacted]	£3,102.84	Assumed to be same as pneumonia (TA395)[95]

Febrile neutropenia	[redacted]	[redacted]	[redacted]	£7,045.41	Brown *et al*[88]
Bronchitis	[redacted]	[redacted]	[redacted]	£171.14	Assume the same as lower respiratory tract infection¤
Platelet Count Decreased	[redacted]	[redacted]	[redacted]	£577.66	TA428[89]
Weight decreased	[redacted]	[redacted]	[redacted]	£0.00	Assume same as decreased appetite (TA428)[89]
Hypothyroidism	[redacted]	[redacted]	[redacted]	£0.00	Assumption
Hypokalaemia	[redacted]	[redacted]	[redacted]	£465.00	NHS Reference Costs 16/17[87*]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	£465.00	NHS Reference Costs 16/17[87*]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	£0.00	Assumed to be zero
Headache	[redacted]	[redacted]	[redacted]	£0.00	Assumed to be zero
Paraesthesia	[redacted]	[redacted]	[redacted]	£0.00	Assumed to be zero
Hypotension	[redacted]	[redacted]	[redacted]	£0.00	Assumed to be zero
Hypocalcemia	[redacted]	[redacted]	[redacted]	£465.00	NHS Reference Costs 16/17[87*]

Source: CS[l] and company's model
Note: Some of the items have been inflated to 2016/17 using PSSRU inflation indices[103], § - WJ07B Fever of Unknown Origin with Interventions, with CC Score 0-3; - KC05G: Fluid or Electrolyte Disorders, with Interventions, with CC Score 5+, ¤ - Consultant led follow up visit - Medical oncology. Service code 370 2015-16 costs (TA492)[96]*

Appendix 3: Goodness-of-fit statistics and survivor functions for standard parametric models and spline models fitted to time-to-event data from KEYNOTE-407 by the ERG

Table 51: AIC and BIC statistics, ERG-fitted OS models

Goodness-of-fit, OS, KEYNOTE-407 ITT population				
Model (OS)	**Pembrolizumab combination therapy**		**Carboplatin plus paclitaxel/nab-paclitaxel**	
	AIC	**BIC**	**AIC**	**BIC**
Generalised gamma	983.75	994.63	1274.87	1285.79
Gamma	983.79	991.04	1273.71	1280.98
Log normal	990.24	997.50	1287.57	1294.85
Log logistic	985.64	992.90	1276.06	1283.33
Weibull	983.29	990.55	**1273.15**	**1280.43**
Gompertz	**981.94**	**989.20**	1273.96	1281.24
Exponential	986.17	989.80	1277.21	1280.85
Spline k=1,scale=hazard	984.81	995.69	1274.42	1285.34
Spline k=2,scale=hazard	986.30	1000.81	1276.09	1290.64
Spline k=3,scale=hazard	987.44	1005.58	1274.78	1292.97
Spline k=1,scale=normal	986.12	997.00	1274.43	1285.35
Spline k=2,scale=normal	986.32	1000.83	1275.98	1290.53
Spline k=3,scale=normal	986.79	1004.93	1274.62	1292.81
Spline k=1,scale=odds	986.06	996.94	1273.85	1284.76
Spline k=2,scale=odds	986.96	1001.47	1275.78	1290.33
Spline k=3,scale=odds	987.87	1006.01	1274.87	1293.06
Goodness-of-fit, PFS, KEYNOTE-407 ITT population				
Model (PFS)	**Pembrolizumab combination therapy**		**Carboplatin plus paclitaxel/nab-paclitaxel**	
	AIC	**BIC**	**AIC**	**BIC**
Generalised gamma	1470.34	1481.22	1716.72	1727.64
Gamma	1468.72	1475.98	1714.89	1722.16
Log normal	1477.35	1484.61	1734.34	1741.61
Log logistic	1465.77	**1473.03**	1712.43	1719.71
Weibull	1470.29	1477.55	1717.59	1724.87
Gompertz	1479.95	1487.21	1734.95	1742.23
Exponential	1483.17	1486.80	1741.29	1744.93
Spline k=1,scale=hazard	1471.63	1482.52	1718.47	1729.39
Spline k=2,scale=hazard	1463.31	1477.82	1709.91	1724.46
Spline k=3,scale=hazard	1458.25	1476.39	1697.38	1715.57
Spline k=1,scale=normal	N/a	N/a	1710.45	1721.37
Spline k=2,scale=normal	1466.71	1481.22	1712.01	1726.56
Spline k=3,scale=normal	**1457.91**	1476.05	1697.41	1715.60
Spline k=1,scale=odds	1465.72	1476.61	1706.61	1717.52
Spline k=2,scale=odds	1464.95	1479.46	1708.75	1723.30
Spline k=3,scale=odds	1457.99	1476.13	**1696.94**	**1715.13**

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

** Best fitting models (lowest AIC/BIC) presented in bold*

Figure 39: ERG-fitted standard parametric models, OS, pembrolizumab combination therapy

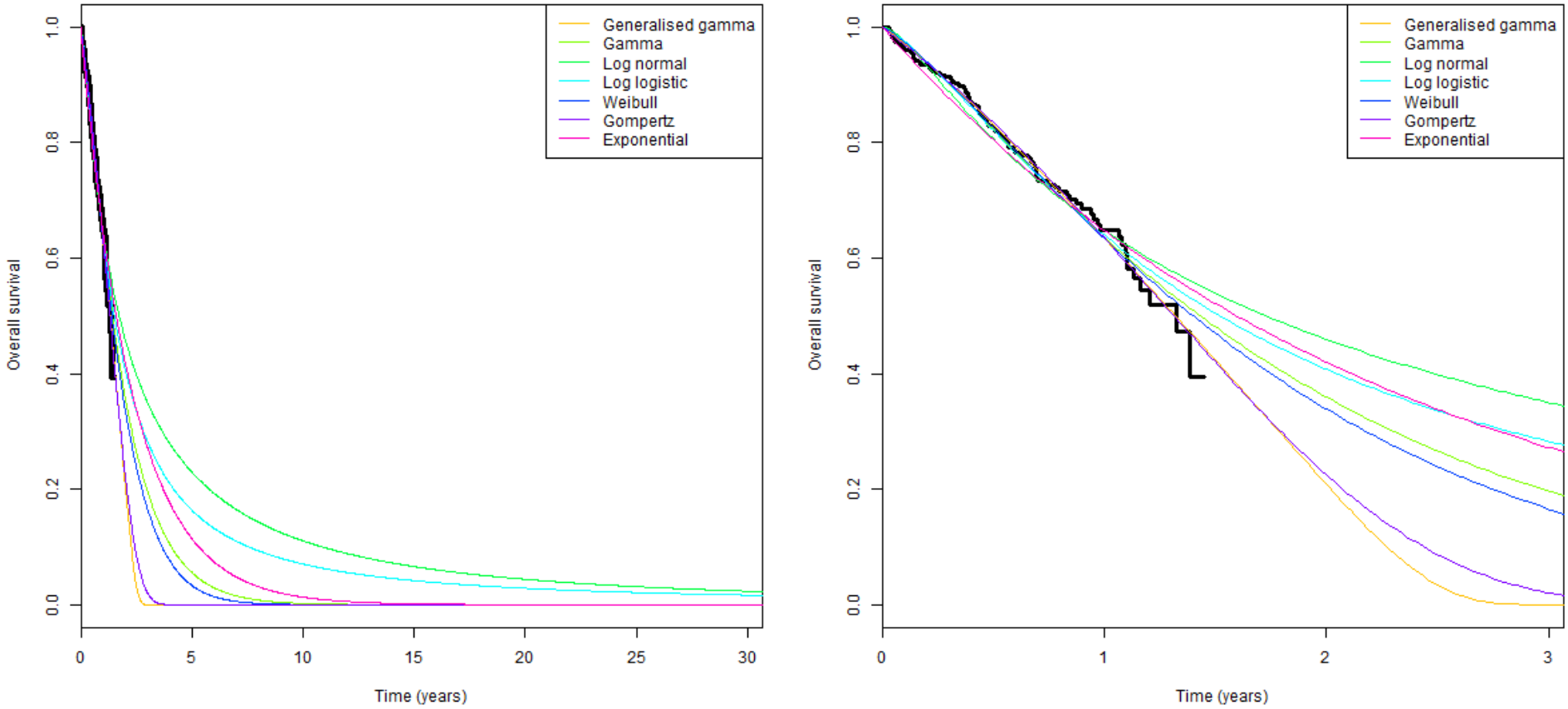


Figure 40: ERG-fitted spline models, OS, pembrolizumab combination therapy

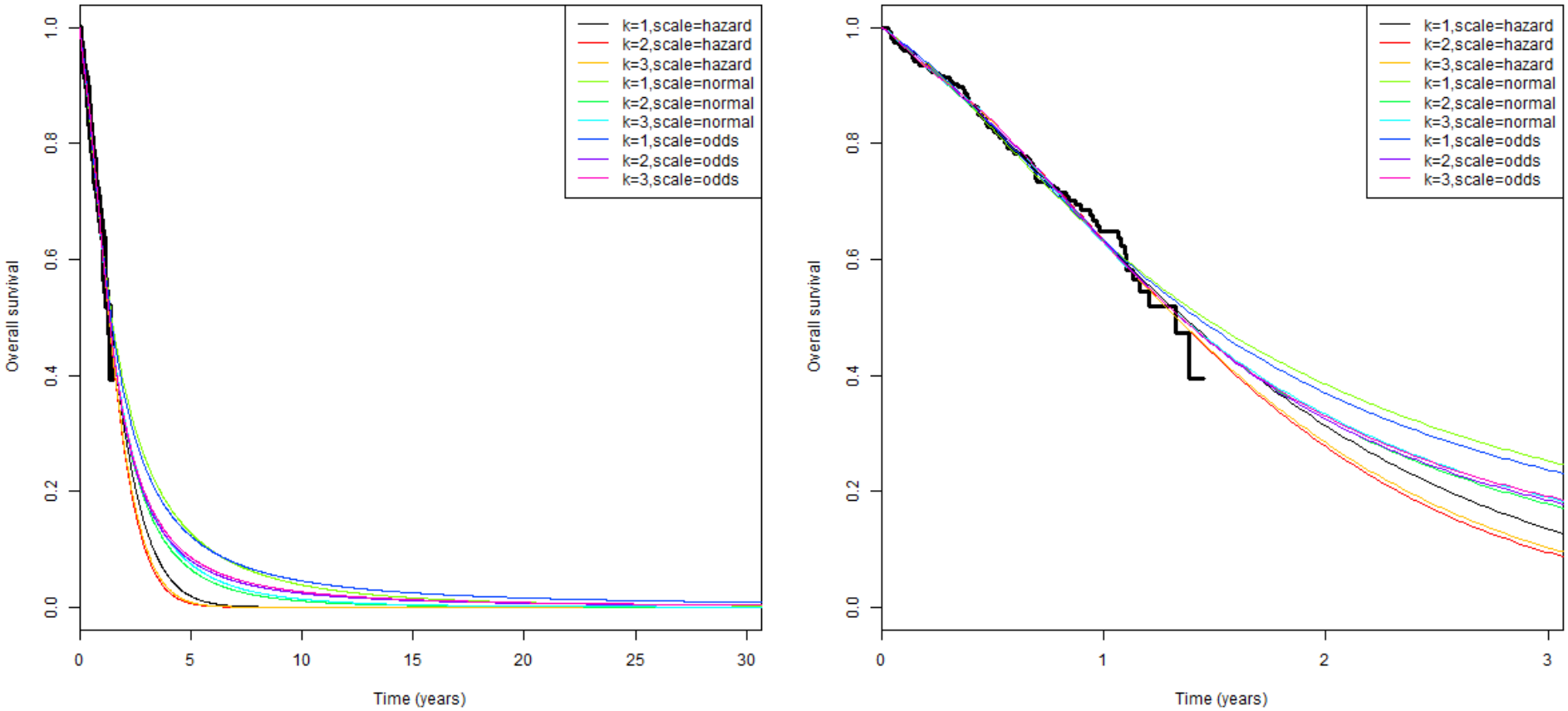


Figure 41: ERG-fitted standard parametric models, OS, carboplatin plus paclitaxel/nab-paclitaxel

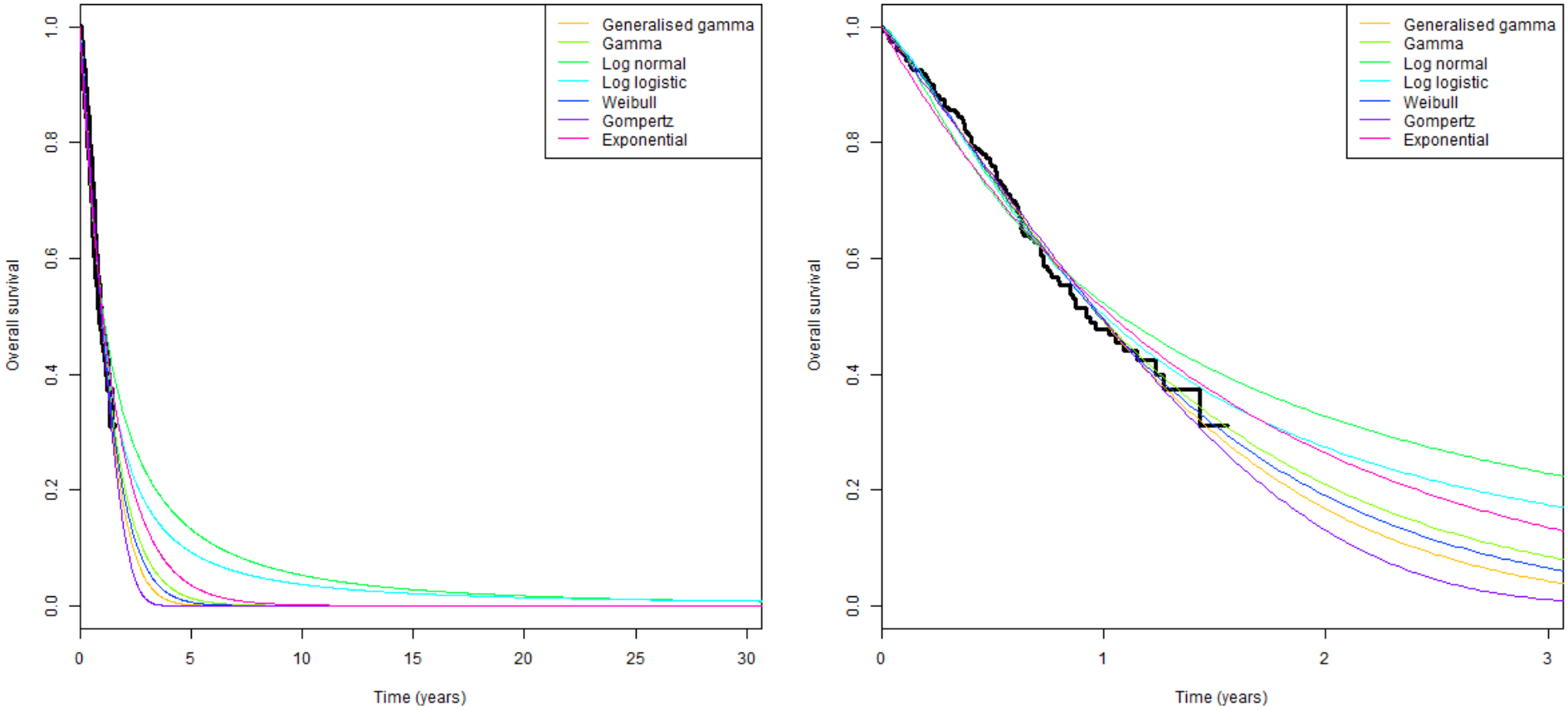


Figure 42: ERG-fitted spline models, OS, carboplatin plus paclitaxel/nab-paclitaxel

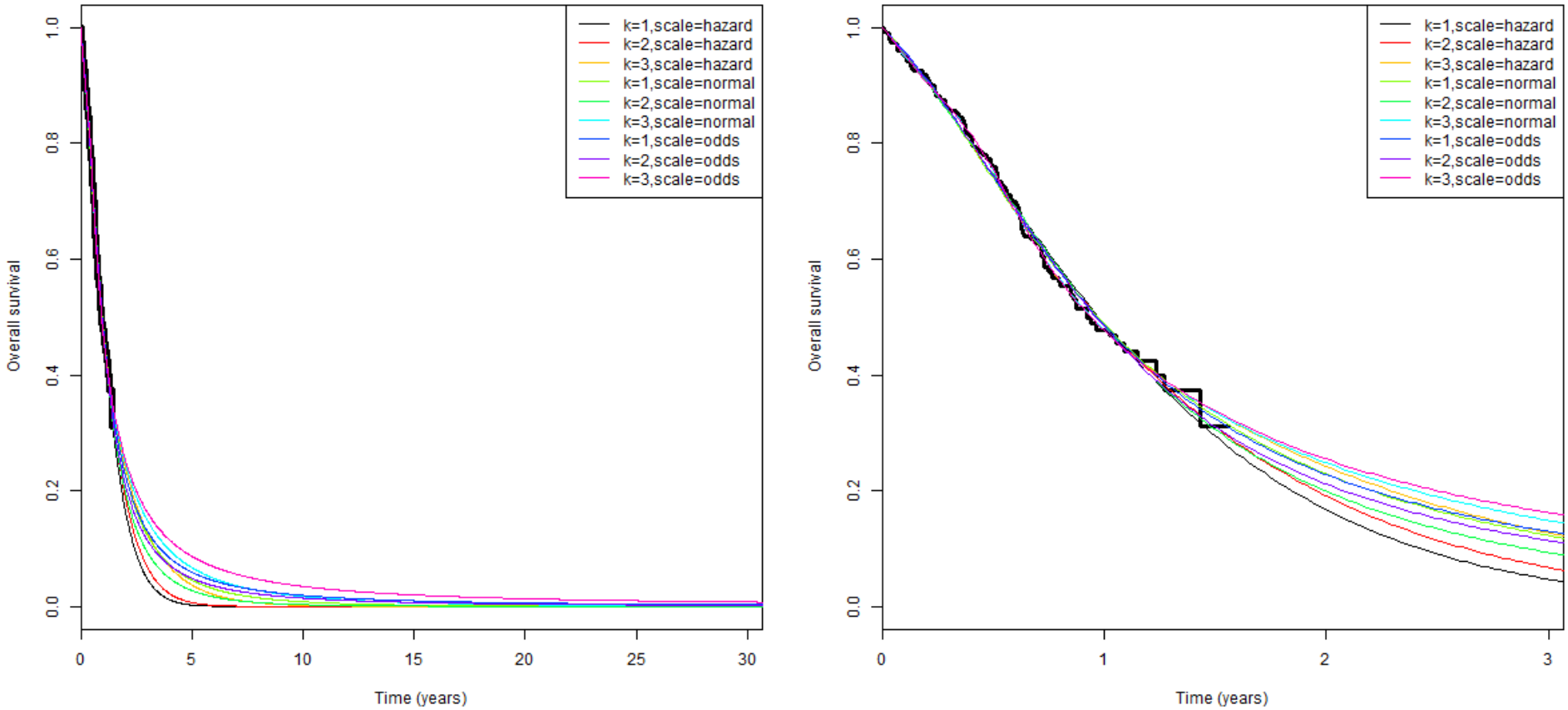


Figure 43: ERG-fitted standard parametric models, PFS, pembrolizumab combination therapy

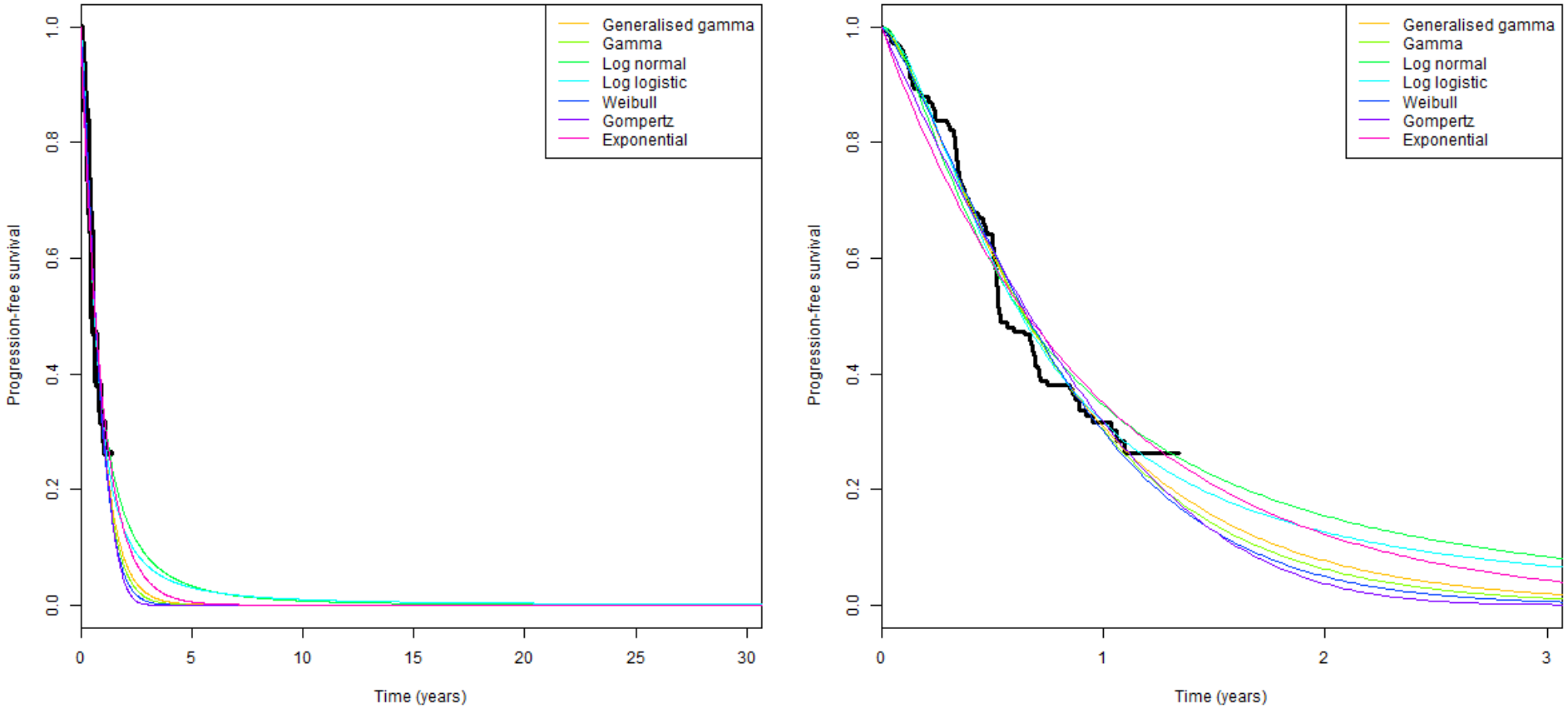


Figure 44: ERG-fitted spline models, PFS, pembrolizumab combination therapy

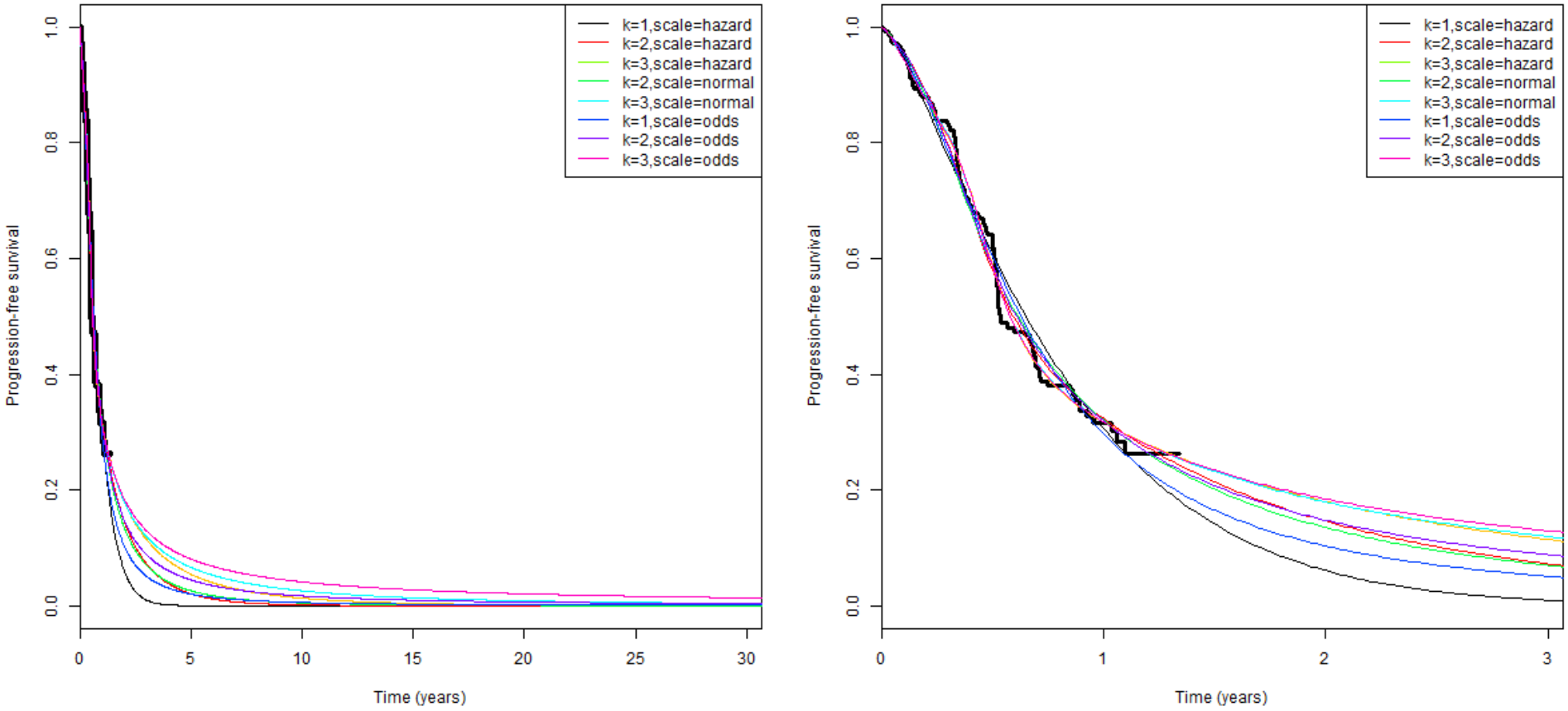


Figure 45: ERG-fitted standard parametric models, PFS, carboplatin plus paclitaxel/nab-paclitaxel

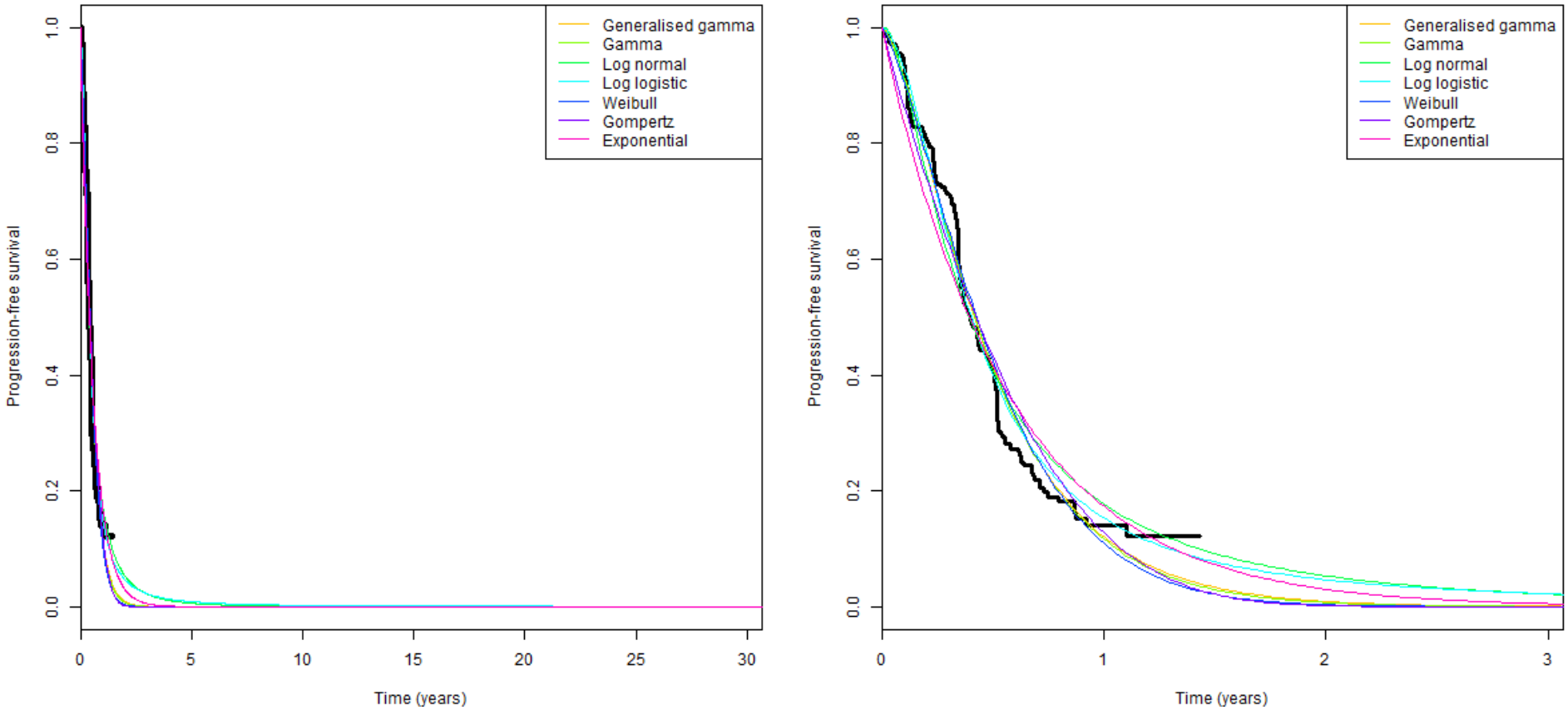
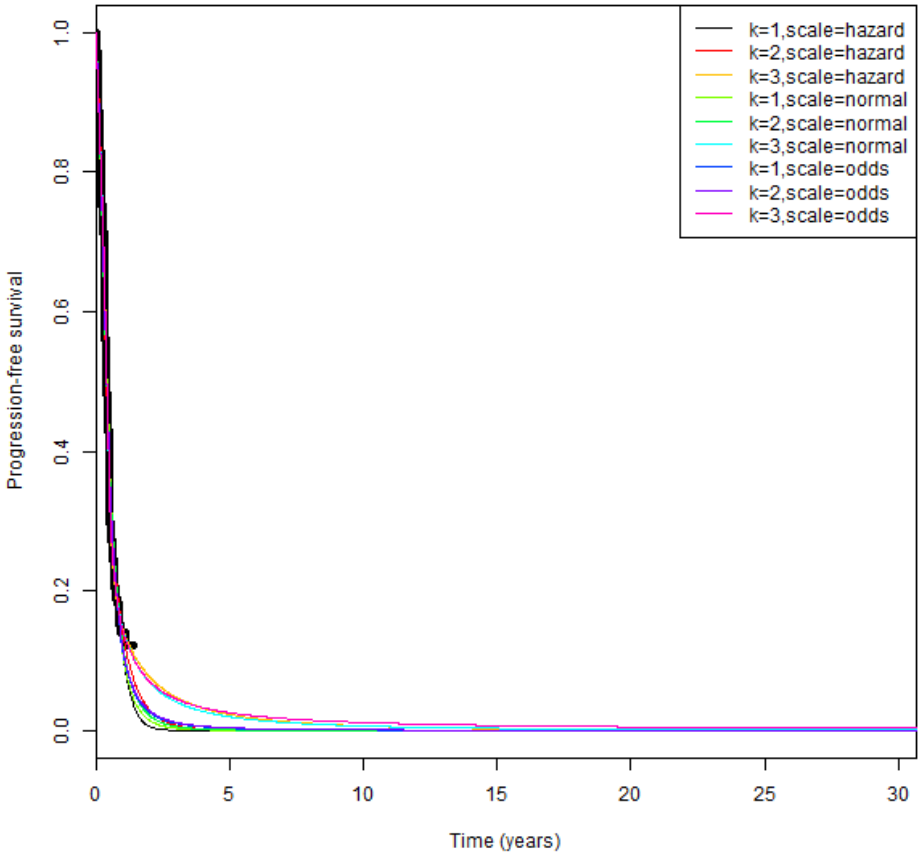
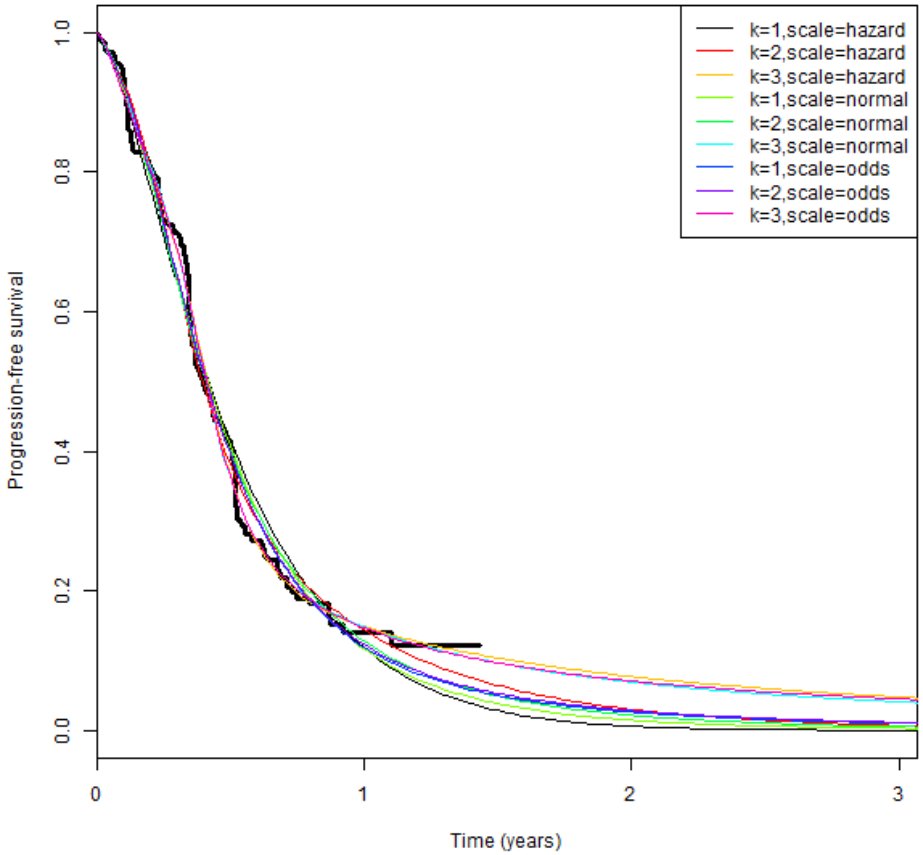


Figure 46: ERG-fitted spline models, PFS, carboplatin plus paclitaxel/nab-paclitaxel





Appendix 4: **Technical appendix detailing methods for implementing the ERG's exploratory analyses**

Exploratory analysis 1- Correction of errors

(a) Correction of OS functions for NMA comparators.

Replace the value in worksheet "Modeled OS" cell Y9 with formula "=V9^'NMA-ITC OS (conHR)'!$O$19". Drag the formula down to the bottom of the array.

Replace the value in worksheet "Modeled OS" cell Z9 with formula "=V9^'NMA-ITC OS (conHR)'!$O$20". Drag the formula down to the bottom of the array.

Replace the value in worksheet "Modeled OS" cell AA9 with formula "=V9^'NMA-ITC OS (conHR)'!$O$21". Drag the formula down to the bottom of the array.

(b) Correction of HR for pembrolizumab monotherapy comparison

Replace the value in worksheet "NMA-ITC OS (conHR)" cell O50 with value "=1/0.97".

(c) Amendment of AE calculations

Replace the formula in worksheet "AE Costs UK" cell C58 with formula "=SUMPRODUCT(Parameters!Q89:Q140,Parameters!Q251:Q302)".

Replace the formula in worksheet "AE Costs UK" cells D58 with formula "=SUMPRODUCT(Parameters!Q143:Q194,Parameters!Q251:Q302)".

Replace the formula in worksheet "AE Costs UK" cells E58 with formula "=SUMPRODUCT(Parameters!Q197:Q248,Parameters!Q251:Q302)".

(d) Consistent application of a half-cycle correction

Replace the formula in worksheet "Cohort simulation" cell AX11 with formula *"=(L11+Pembro_Chemo_2L_Use*(1-L11-Q11))*cost_PFstatePembro+(1-Pembro_Chemo_2L_Use)*(1-L11-Q11)*cost_PDstate".* Drag the formula down to the bottom of the array.

Exploratory analysis 2 - Use of HRQoL based on progression status

Apply all changes from ERG exploratory analysis 1.

Go to worksheet "Utility Inputs", click on dropdown menu on cell E5:F5, choose the option "Utility by progression status".

Replace the value in worksheet "Parameters" cell C33 with a value of 0.605121898.

Replace the value in worksheet "Parameters" cell C36 with a value of 0.615365882.

These values are based on the information provided in the table and the equations below.

Parameter name	Value
p_1stIO2ndchemo	0.27
p_1stIO2ndIO	0.00
p_1stchemo2ndIO	0.40
p_1stchemo2ndchemo	0.12
d_2ndLPFtimepembro	0.32
d_2ndLPFtimechemo	0.48
PFSutility_alltreat	[redacted]
PDutility_alltreat	0.58

Equation for post-progression utility for pembrolizumab group
'=((p_1stIO2ndIO*d_2ndLPFtimepembro*PFSutility_alltreat)+(p_1stIO2ndchemo*d_2ndLPFtimechemo*PFSutility_alltreat)+(p_1stIO2ndIO*(1-d_2ndLPFtimepembro)*PDutility_alltreat)+(p_1stIO2ndchemo*(1-d_2ndLPFtimechemo)*PDutility_alltreat)+((1-p_1stIO2ndIO-p_1stIO2ndchemo)*PDutility_alltreat))'

Equation for post-progression utility for SC chemotherapy group
'=((p_1stchemo2ndIO*d_2ndLPFtimepembro*PFSutility_alltreat)+(p_1stchemo2ndchemo*d_2ndLPFtimechemo*PFSutility_alltreat)+(p_1stchemo2ndIO*(1-d_2ndLPFtimepembro)*PDutility_alltreat)+(p_1stchemo2ndchemo*(1-d_2ndLPFtimechemo)*PDutility_alltreat)+((1-p_1stchemo2ndIO-p_1stchemo2ndchemo)*PDutility_alltreat))'

Exploratory analysis 3 - Disease management costs based on PFS/PPS
Apply all changes from ERG exploratory analysis 1.
Replace the formula in worksheet "Cohort simulation" cell AX11 with
*'=(M11*PFScost_mgt)+(O11*((p_1stIO2ndIO*d_2ndLPFtimepembro*PFScost_mgt)+(p_1stIO2ndchemo*d_2ndLPFtimechemo*PFScost_mgt)+(p_1stIO2ndIO*(1- d_2ndLPFtimepembro) * PDcost_mgt) + (p_1stIO2ndchemo * (1 - d_2ndLPFtimechemo) * PDcost_mgt) + ((1 - p_1stIO2ndIO - p_1stIO2ndchemo) * PDcost_mgt)))',*

where
PFScost_mgt = 89.5343317
PDcost_mgt = 144.3253151
p_1stIO2ndIO = 0
p_1stIO2ndchemo = 0.27388535
d_2ndLPFtimepembro = 0.321052632
d_2ndLPFtimechemo= 0.482758621
Drag the formula down to row 2,098.

Replace the formula in worksheet “Cohort simulation” cell DD11

with

*‘=(BS11*PFScost_mgt)+(BU11*((p_1stchemo2ndIO*d_2ndLPFtimepembro*PFScost_mgt)+(p_1stchemo2ndchemo*d_2ndLPFtimechemo*PFScost_mgt)+(p_1stchemo2ndIO*(1-d_2ndLPFtimepembro)*PDcost_mgt)+(p_1stchemo2ndchemo*(1-d_2ndLPFtimechemo)*PDcost_mgt)+((1-p_1stchemo2ndIO-p_1stchemo2ndchemo)*PDcost_mgt)))’,*

where

PFScost_mgt = 89.5343317
PDcost_mgt = 144.3253151
p_1stchemo2ndIO= 0.399038462
p_1stchemo2ndchemo= 0.120192308
d_2ndLPFtimepembro= 0.321052632
d_2ndLPFtimechemo= 0.482758621

Drag the formula down to row 2,098.

Exploratory analyses 4 - Second-line immunotherapy treatment costs doubled

Apply all changes from ERG exploratory analysis 1.

Go to worksheet “Regimen Costs UK”.

Replace the value in cell D147 with the formula “=(75/2)*2”.

Replace the value in D150 with the formula “=(102/2)*2”.

Exploratory analyses 5a - Alternative PFS and OS models - Optimistic scenario

Apply all changes from ERG exploratory analysis 1.

Go to worksheet “Pembro Chemo OS”. Copy the values in worksheet cells M9:M2096.

Go to worksheet “Modeled OS”. Paste those values to cells V9:V2096.*Exploratory analyses 5b - Alternative PFS and OS models - Pessimistic scenario*

Apply all changes from ERG exploratory analysis 1.

Go to the file ‘ERG curve fitting – KEYNOTE-407’ provided.

Copy the cumulative survival probabilities of the ERG’s log logistic model for pembrolizumab in combination. Go to worksheet “Modeled OS” in the model and paste these values to cells V9:V2096.

Go to the file ‘ERG curve fitting – KEYNOTE-407’ provided.

Copy the cumulative survival probabilities for the ERG’s log logistic model for SC chemotherapy. Go to worksheet “Modeled OS” in the model and paste these values to cells W9:W2096.

Exploratory analyses 6 - Optimistic and pessimistic scenarios ERG-preferred analysis (deterministic)
For optimistic scenario 6a, apply all changes from ERG exploratory analyses 1-5a, as described above. For pessimistic scenario 6b, apply all changes from ERG exploratory analyses 1-5b, as described above.
Additional sensitivity analysis and subgroup analysis should start from these versions of the model (optimistic and pessimistic).

Additional sensitivity analysis 1: Increased proportion costs of second-line immunotherapy
Replace the values in worksheet "Regimen Costs UK" cells C117:D117 with the value "0.75". Note – these proportions need to be applied to the progression-based utility equations as well.

Additional sensitivity analysis 2: Impacts of AEs on HRQoL and costs doubled for pembrolizumab combination therapy group
Replace the formula in worksheet "Cohort simulation" cell AO11 with formula "=-IF(C11=0,'Utility Inputs'!$D$36,0)*2".
Replace the formula in worksheet "Cohort simulation" cell BD11 with formula "=*p.AEcost.PembroChemo**2".

Additional sensitivity analysis 3: Fully incremental analysis including NMA comparators
Perform a fully incremental analysis from the results in 'Results' worksheet using ERG exploratory analyses 6a and 6b.

Additional sensitivity analysis 4: Exploration of all parametric models fitted by the ERG
Go to the file 'ERG curve fitting – KEYNOTE-407' provided.
Copy the values of each of the ERG's OS models for pembrolizumab in combination. Copy the values for the same model type for SC. Go to worksheet "Modeled OS" in the model and paste the values to cells V9:V2096 and W9:W2096, respectively.

Additional sensitivity analysis 5: Subgroup analyses by PD-L1 subgroup
For each subgroup:
Go to worksheet "Model Settings", click on dropdown menu on cell I21, choose the relevant PD-L1 TPS subgroup.
Select the appropriate optimistic and pessimistic curves for the selected subgroup (optimistic – from company's model; pessimistic from file 'ERG curve fitting – KEYNOTE-407').
For the PD-L1 TPS ≥50% subgroup, change the TTD function to the exponential.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]

You are asked to check the ERG report from School of Health and Related Research (ScHARR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Wednesday 30 January** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Pages 12, 13, 14, 44, 48, 50, 58: ERG cites concerns relating to the NMA in the CS, in particular that the NMA does not accurately reflect current clinical practice as none of the trials included second-line immunotherapy	Please add wording to the effect of: However, this is due to the fact that the published studies on comparator efficacy pre-date the availability of immunotherapy treatment options.	The wording suggests this is an omission in the CS; in reality the published literature on the comparator products pre-dates the availability of immunotherapy treatment options and therefore could not be included.	This is not a matter of factual inaccuracy. When conducting a literature review and subsequent evidence synthesis, the population, intervention, comparator and outcome (PICO) included should reflect PICO in the decision problem under consideration. Any discrepancy should be clearly stated and the rational for inclusion provided. The ERG's concerns reflect this issue. No changes have been made.
Page 31: ERG queried why there was a difference in confidential date for final analysis provided by the company compared with the study completion date published in CT.gov	Suggest remove this sentence.	Final analysis and completion of the study are different. Final analysis is as per the protocol when the pre-specified number of OS and PFS events are reached whereas study completion date relates to the final date on which data are collected (last patient, last visit).	The ERG agrees that the last part of the sentence "which is [redacted] than the estimated date reported in the CS" does infer reference to the final analysis. This phrase has been removed from the sentence.
Page 31: exclusion criteria – …'completed palliative	Amend to: …completed	As per CSR stated exclusion criteria	Apologies. Page 37 amended

therapy within 7 days'	palliative radiotherapy within 7 days…		
Page 37: Progression-free survival sub-section, line 8 of paragraph; data error	Text currently reads: …months) compared with 4.8 months (95% CI from 43 to 5.7)… Amend 43 to 4.3 as below: …months) compared with 4.8 months (95% CI from 4.3 to 5.7)…	To correct original error in the text of the CS which was transcribed into the ERG report.	Apologies. Page 37 amended.
Page 43: ITC1, NMA1: Squamous, PD-L1 unselected paragraph ERG notes that 'it is unclear how the relevant data from ECOG 1594 were extracted due to the fact that this trial recruited both patients with squamous and non-squamous histology.'	Suggest remove this sentence	ECOG 1594 trial did recruit squamous and non-squamous patients, however, OS and PFS results from the study were stratified by histology and hence data specifically for the non-squamous population were readily available for inclusion in the NMA as detailed in Table 32 of the CS (page 83) (Source: Table 2 of the reference Hoang et al 2013 which was included in the reference pack with the CS.)	Page 43 amended as suggested.

Page 55; paragraph 3 In relation to the rationale provided at clarification questions stage as to why KN024 was not included in the ITC (‘*the trial population of patients with squamous histology who received paclitaxel + carboplatin chemotherapy was very small (n=5 in each treatment arm’)*, ERG comments: ‘It is unclear why the CS only considered patients who received carboplatin + paclitaxel and what “*each treatment arm*” referred to’	Suggest remove the sentence: ‘It is unclear why the CS only considered patients who received carboplatin + paclitaxel and what “*each treatment arm*” referred to’	The rationale for only considering patients who received carboplatin plus paclitaxel is as detailed in the Appendix D1.2.3.2 of the CS, which describes the methodology of the ITC. The last paragraph of page 150 states …’in order to have a common control arm that can serve as an anchor in the ITC, only patients with squamous histology who had been pre-assigned to paclitaxel + carboplatin…were selected.’ ‘Each treatment arm’ refers to the two treatment arms in KN024; i.e. pembrolizumab monotherapy and chemotherapy control.	This is not a matter of factual inaccuracy as the ERG represented the information as presented. The statement in the last paragraph of page 150 only refers to KEYNOTE-042 and KEYNOTE-407. “In order to have a common control arm that can serve as anchor in the ITC, patients pre-assigned to paclitaxel + carboplatin chemotherapy from KEYNOTE-042 and KEYNOTE-407 and to nab-paclitaxel + carboplatin chemotherapy from KEYNOTE-407 were selected.” There is a discrepancy between the reported number of squamous histology patients who received pembrolizumab monotherapy. The study publication Reck et al. (2016) reported 29; whereas 5 patients were reported here. No changes were made.
Page 75: The methods by which the company estimated OS outcomes for the NMA comparators	Suggest remove this sentence	Details of the methods used to estimate OS and PFS outcomes for the NMA comparators were presented in Appendix D1.2.3, pages 118-122 of the CS. In addition, the full NMA report was provided in the submission pack	This is not factually inaccurate. This sentence within the ERG report was referring to the unusual calculations used to estimate

in the model were not described in the CS		as a reference. Details of modelling long tern effectiveness estimates for indirect comparators was provided in the company appendix L.	cumulative survival probabilities for the NMA comparators (Worksheet “Modeled OS” columns Y:AA). These are not described in the CS or its appendices. The text has been amended to state “The methods by which the company estimated cumulative OS probabilities for the NMA comparators in the model were not described in the CS”
Page 89: The ERG notes that this HR does not match the ITC results reported in the CS;1 this error is further detailed in Section 5.3.3).	Add “However, this was addressed and amended in clarification questions”	As it was corrected, this provides context to the process and has been mentioned elsewhere with regards to this comment from the ERG (page 61, 67, 69).	This is not a factual inaccuracy. For the sake of clarity, the text has been amended to note that the error was amended during the clarification stage.
Page 99 states: Within the PD-L1 TPS ≥50% subgroup, a fully incremental analysis of the available options suggests that pembrolizumab combination therapy is ruled out due to extended dominance (by pembrolizumab monotherapy and carboplatin+paclitaxel/nab-paclitaxel). As the	Suggest to remove “As the company’s submitted model uses an incorrect HR for this analysis, the ERG believes that the results for this subgroup are invalid and should be	As part of the clarification responses, MSD accepted this error and submitted an updated model with this corrected. The ERG therefore are able to review this result with the corrected ITC value hence the subgroup results should not be disregarded entirely.	This is not a factual inaccuracy. The results are invalid. For the sake of clarity, the text has been amended to point to the corrected results in Section 5.3.3.

company's submitted model uses an incorrect HR for this analysis, the ERG believes that the results for this subgroup are invalid and should be disregarded.	disregarded."		
In Table 32: "The subgroup analysis in patients with PD-L1 TPS≥50% includes relative utility multipliers for the pembrolizumab monotherapy group. No explanation or justification of this approach is given in the CS or the CS appendices"	Remove "No explanation or justification of this approach is given in the CS or the CS appendices"	Page 151 of the CS reads: The above described utility measures were also modelled for pembrolizumab monotherapy. Utility values could differ for pembrolizumab monotherapy, as the absence of a chemotherapy regimen and associated quality of life impacts could favourably impact utilities. Therefore, EQ-5D utility data were utilised from the KEYNOTE-024 trial of pembrolizumab monotherapy versus chemotherapy in metastatic NSCLC. Because patient characteristics may differ between patients in KEYNOTE-024 and KEYNOTE-407, rather than incorporating KEYNOTE-024 utilities directly, the ratio of utilities for the pembrolizumab monotherapy as compared to the chemotherapy arm in KEYNOTE-024 was first estimated for each health state and then multiplied by the utility values assumed for the	The ERG partially agrees. The text has been amended to clarify that whilst the utility ratio approach was described, no justification was provided for assuming the same utility values for time to death categories in the pembrolizumab combination therapy and the chemotherapy groups, and different utility values for time to death categories in the pembrolizumab monotherapy group. If these ratios are intended to reflect impacts of AEs, these should already be captured in the modelled QALY losses associated with AEs.

		corresponding health state for patients in the chemotherapy arm in KEYNOTE-407. Effectively, this method normalises the estimated utility values for pembrolizumab monotherapy patients so that the relationship in utilities relative to chemotherapy patients is preserved when comparing to KEYNOTE-407 values (**Error! Reference source not found.**).	
Page 106: "In response to a request for clarification on this issue from the ERG (clarification response,12 question B31), the company stated "The data in column AK, and on the worksheet generally, only reflect implementation of the parametric extrapolation approach for the indirect comparators. The SEER-based approach is implemented for the indirect treatment comparators on the 'Modeled OS' worksheet in the formulae in columns Y to AA. Therefore there is	Remove this section of text.	The ERG is mistaken. The NMA HRs are applied to the SEER data in columns Y to AA on the Modeled OS worksheet as I had previously described and as can be seen in columns F-H and P-R of that worksheet and the relevant columns for modelling Death (Cumulative) on the Cohort Simulation worksheet, the SEER data are fed through the model.	The company is incorrect. The cumulative OS probabilities for the NMA comparators in the "NMA-ITC OS (conHR) " worksheet are dependent on the pembrolizumab combination therapy OS function. This is contained in column AK. This is the baseline to which the HRs are applied (although these are then incorrectly applied in the "modeled OS" worksheet). Changing the cumulative OS probabilities for the baseline changes the cumulative OS probabilities for the NMA comparators. This baseline is erroneously using the KM/exponential function rather than the KM/SEER. This is clearly

not an error." The ERG believes that the company's response is incorrect: the formulae in column AK are fed through the model and these directly impact on the ICERs of pembrolizumab combination therapy versus all of the NMA comparators."			incorrect. No amendment has been made to the ERG report.
Page 75: Given that the HRs applied in the model are greater than 1.0, this would indicate that these were intended to be applied to the pembrolizumab combination therapy group as a baseline (by raising the cumulative OS probabilities to the power of the HR). This is the approach taken to apply relative treatment effects for PFS in the company's model. However, the calculations used to apply OS treatment effects in the company's original	Add "This issue was corrected and updated analysis provided as part of the clarification questions"	As it was corrected, this provides context to the process and has been mentioned elsewhere with regards to this comment from the ERG (page 61, 67, 69).	This is not factually inaccurate. As noted in the company's comment, the report states that this issue has been corrected elsewhere. We have not corrected the text here because it may mislead the reader into believing that Figure 8 includes the corrections.

submitted model are unusual and use modelled projections from the trial comparator group rather than the intervention group. The ERG believes that this aspect of the company's model is subject to errors which invalidate the results of Base Case Analysis 2; the curves presented in **Error! Reference source not found.** which use functions from the company's original submitted model (prior to correction), should therefore be interpreted with caution. These errors are described in detail in Section 5.3.3.			
Page 54: The ITC HRs used in the economic model do not match these results; the ERG is unclear regarding the source of the values applied in the company's model; this issue is further discussed	Add "This issue was corrected and updated analysis provided as part of the clarification questions"	As it was corrected, this provides context to the process and has been mentioned elsewhere with regards to this comment from the ERG (page 61, 67, 69).	This is not factually inaccurate. This correction is mentioned several times elsewhere in the report. No amendment has been made to the report.

in Section 5.3.3.			
Page 59: This was based on a published NICE filter modified by: (a) the inclusion of terms referring to Ireland - which will only increase the sensitivity of the search, and (b) the application of an exclusion clause (at line 80). This latter modification is of particular concern as it contains an error which may have accidentally excluded studies relating to the constituent nations of the UK. The syntax excludes papers indexed with the heading "Europe", with the exception of those indexed "United Kingdom"; however, as the "United Kingdom" heading is not used in its exploded form, papers indexed as "England", "Scotland", "Northern Ireland" or "Wales" remain excluded. Given the limited time	Remove this section or amend as appropriate.	The ERG has suggested that MSD added an exclusion clause whilst this is not the case since this is part of the NICE filter (reference for this: The development of validated UK geographic search filters for MEDLINE and Embase, NICE presentation available at: https://archive.cilip.org.uk/sites/default/files/documents/amy_finnegan_team_0.pdf). MSD note the concern and have re-run the analysis using the exploded UK sub heading (i.e. “united kingdom/” instead of “exp united kingdom/”) which returned one further irrelevant paper (Chaddha U, et al. Effect of language and ethnicity on interval from diagnosis to treatment in non-small cell lung cancer patients at a public and a private hospital. CHEST 2017 Annual Meeting. Canada. 152 (4 Supplement 1) (pp A620), 2017)	The text has been removed.

available within the STA process, it was not feasible for the ERG to re-run the searches, sifting and study selection with these errors corrected, hence their implications are unclear.			
Page 82: The CS does not provide any details regarding how the utility values for pembrolizumab monotherapy for the time-to-death utility categories (applied as ratios) were estimated.	Remove these sentences	Details of this are given on page 151 of the CS and Table 67	The text has been amended to note that no justification is provided for assuming different utilities by time-to-death category.
Page 104: The subgroup analysis in patients with PD-L1 TPS≥50% includes relative utility multipliers for the pembrolizumab monotherapy group. No explanation or justification of this approach is given in the CS or the CS appendices.	Remove these sentences	Details of this are given on page 151 of the CS and Table 67	This is repetition of a previous comment. See above.

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer: A Single Technology Appraisal

ERG additional analyses around atezolizumab list price

Aline Navega Biz
Lesley Uttley
Paul Tappenden
School of Health and Related Research (ScHARR)

23th April 2019

This addendum provides additional exploratory analyses, which include the list price for atezolizumab.

Analyses have been conducted only for the ERG's preferred pessimistic scenarios, assuming the same characteristics of the analyses performed on the previous addendum (from 15th April). The analyses were undertaken separately for the overall population and for each PD-L1 subgroup (Table 1).

Table 1: ERG-preferred pessimistic analyses by TPS subgroups

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Overall population							
Pembrolizumab combination	3.23	1.91	£60,457	1.06	0.65	£28,181	**£43,224**
Standard chemotherapy	2.17	1.26	£32,276	-	-	-	-
PD-L1 TPS <1% subgroup							
Pembrolizumab combination	3.29	1.85	£59,485	1.88	0.93	£30,181	**£32,304**
Standard chemotherapy	1.40	0.92	£29,304	-	-	-	-
PD-L1 TPS 1-49% subgroup							
Pembrolizumab combination	3.12	1.91	£65,331	1.03	0.71	£33,215	**£46,973**
Standard chemotherapy	2.09	1.20	£32,116	-	-	-	-
PD-L1 TPS ≥50% subgroup							
Standard chemotherapy	4.01	2.02	£40,569	-	-	-	**Dominating**
Pembrolizumab combination	3.72	2.01	£61,044	-	-	-	**Dominated**
Pembrolizumab monotherapy	3.56	1.94	£66,382	-	-	-	**Dominated**

ICER - incremental cost-effectiveness ratio; LYG - life year gained; PD-L1 - programmed death-ligand 1; QALY - quality-adjusted life year
** undiscounted*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

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

1. Summary of technical report

1.1 This document is the 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:

- a commentary on the evidence received and written statements
- technical judgements of the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the key evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

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

1.2 After technical engagement the technical team has collated the comments received and, if relevant, updated the scientific judgement by the technical team and rationale. Scientific judgments that have been updated after engagement are highlighted in **bold** below.

1.3 In summary, the technical team considered the following:

- The KEYNOTE 407 trial did not reflect UK clinical practice for people who have a strong PD-L1 expression of ≥50%, as pembrolizumab monotherapy has not been used as a comparator. This increases uncertainty in cost-effectiveness estimates for this group.
  The company's network meta-analyses (NMAs) are not required for decision-making for the PD-L1 <50% subgroup as during technical engagement there was a consensus that the various standard chemotherapy regimens are broadly similar in efficacy. However, the NMA is needed for an indirect treatment comparison between pembrolizumab combination therapy and pembrolizumab monotherapy as monotherapy was not included as a comparator in the KEYNOTE-407 trial. Pembrolizumab monotherapy is standard clinical practice in NHS England for people who have a strong PD-L1 expression of ≥50% (see issue 9 and table 4).
- There is uncertainty regarding the place in the treatment pathway of pembrolizumab combination therapy for people who have a low PD-L1 TPS expression of <1% and people with a PD-L1 TPS of 1-49%, which may impact on the relevance of the cost-effectiveness estimates for these groups (see issue 2). **This issue has been resolved during technical engagement (see table 4).**
- Using a stopping rule of 2 years may be appropriate for this indication (see section 3, table 5).
- Overall survival estimates are a major influence on the Incremental cost-effectiveness ratio (ICER). **Due to the short duration of the interim analysis of KEYNOTE-407, long-term outcomes are highly uncertain.** The company has used the U.S Surveillance Epidemiology

and End Results (SEER) for long term OS extrapolation which has issues surrounding its comparability to standard clinical practice within the UK, **including the lack of second-line treatments. All clinical advisors stated that they believed that using the SEER database, and a relative risk ratio from months 7-12 in the KEYNOTE-407 trial, produced too optimistic overall survival results for the pembrolizumab combination arm of the trial.** (see issue 1).

- The company's assumed lifetime treatment effect is likely to be too optimistic. **It is more realistic to assume a treatment benefit of 3 to 5 years from start of treatment** (see issue 4).
- Using a time to death (TTD) utility approach for capturing changes in health-related quality of life **is not** appropriate for this appraisal. Instead, a model using health states based on disease progression status **is** more appropriate. In addition, a utility value from the literature **(Khan et al)** is likely more appropriate for the progressed disease health state than directly collected progressed disease utility values in KEYNOTE-407 (see issue 6).
- **Pembrolizumab combination therapy is unlikely to meet the criteria for inclusion in the Cancer Drugs Fund because there is no plausible potential for it to be cost-effective, with the current commercial arrangement offered by the company, using the ERG and the NICE technical team's preferred OS modelling approaches (see issue 1). However, if there was a plausible potential for it to be cost-effective, data collection (more mature data from the KEYNOTE-407 trial) would help resolve uncertainty (see Issue 8).**

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

- The clinical trial evidence is immature; median overall survival has not been reached for patients with a PD-L1 expression of TPS ≥50%.

- Outcomes for patients with a low PD-L1 expression of TPS <1% and TPS 1-49% who subsequently received immunotherapy after initial chemotherapy treatment in the control arm of KEYNOTE-407 are highly uncertain. **In addition, the cost-effectiveness modelling does not explicitly include survival benefits of second-line treatments in the standard of care (SoC) arm of KEYNOTE-407 for these subgroups, as only the costs of these treatments are modelled. This is likely to underestimate survival in the SoC arm and underestimate the ICER. The magnitude of influence is unknown (see issue 3).**
- Evidence of long-term adverse events is not captured within the clinical trial evidence presented by the company.

1.5 The cost-effectiveness results for pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer include a commercial arrangement (patient access scheme/commercial access agreement) for pembrolizumab. The company's analyses do not incorporate the patient access scheme for nab-paclitaxel.

1.6 Following technical engagement, the technical team's preferred assumptions result in incremental cost-effectiveness ratios (ICERs) ranging between £33,631 to £45,680 per QALY gained. The technical team note that the most plausible ICER is likely to be above £33,631 and could potentially be above £45,680 due to points presented in issue 3.

1.7 Pembrolizumab combination therapy is unlikely to meet the end of life criteria specified in NICE's guide to the methods of technology appraisal **for the full untreated squamous NSCLC population** (see Issue 7). **Subgroup analysis should be considered both in terms of cost-effectiveness results and in applying NICE's end of life criteria. This is because standard of care in the NHS varies by PD-L1 TPS (see issue 9 – new issue).**

1.8 All relevant benefits associated with pembrolizumab combination therapy are adequately captured in the model (see table 4)

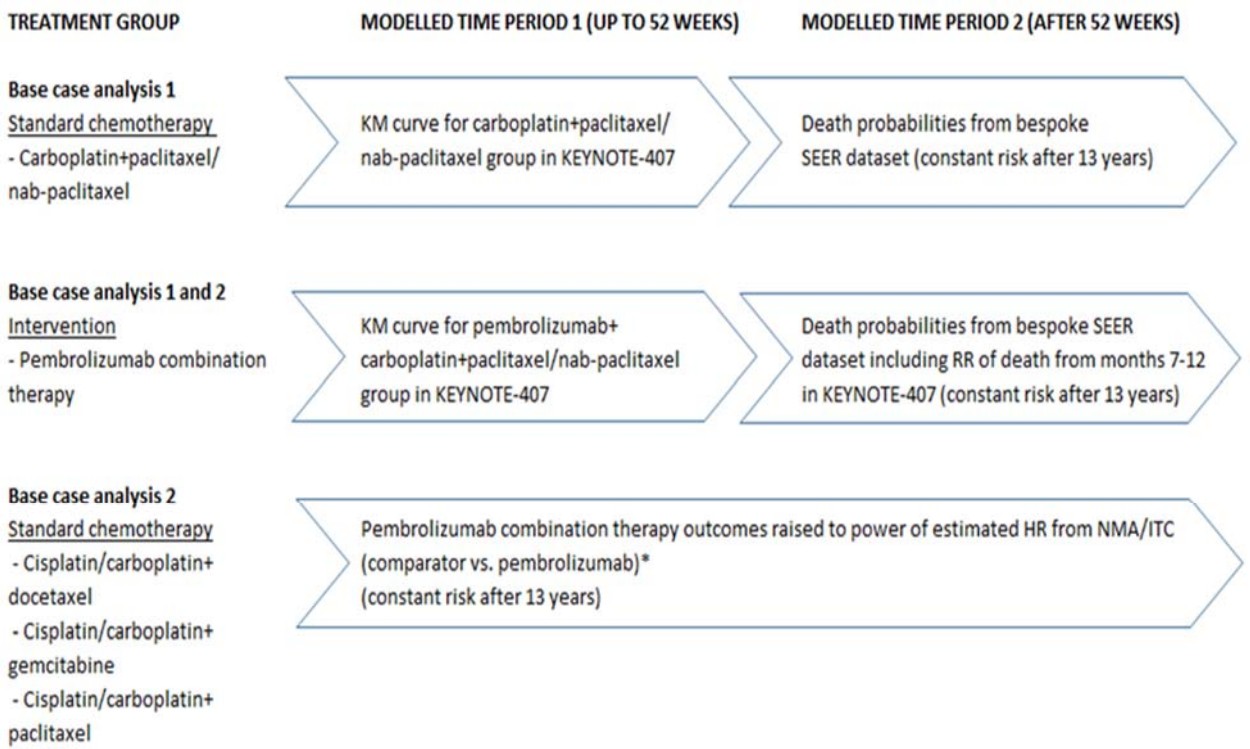
1.9 No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts (see table 4).

2. Key issues for consideration

Issue 1 – Extrapolation of overall survival

Questions for engagement	1. How appropriate is the use of the SEER database to extrapolate long term survival? 2. Would the existing trial data from KEYNOTE-407 be more suitable to use for extrapolation? 3. Which statistical method is preferable to use in when estimating long term outcomes in this population? Would another parametric function be more appropriate? 4. What proportion of patients in the pembrolizumab combination arm would you expect to be alive at 5 and 10 years? What proportion would you expect to be progression-free at these time points? 5. What proportion of patients in the standard of care arm would you expect to be alive at 5 and 10 years? What proportion would you expect to be progression-free at these time points? 6. Is treatment with pembrolizumab combination likely to be curative in some people?
Background/description of issue	**The Company** Follow-up in the KEYNOTE-407 trial interim analysis used in the company's submission is of very short duration. This results in high uncertainty regarding longer term survival. Within its submission, the company has used a bespoke dataset of the U.S Surveillance Epidemiology and End Results (SEER) database to estimate overall survival (OS) beyond the date of the interim analysis cut off in the KEYNOTE-407 trial. The company stated that initially it used parametric models to the Kaplan-Meier (KM) OS data, but this produced clinically implausible OS results for the standard of care arm (1-2% at 5 years using an exponential extrapolation). Further to this, the company states that the mortality risk is time-dependent, and that the observed trial data was sparse.

The company's approach for modelling OS can be seen below:



The company modelled progression-free survival (PFS) using a piece-wise log-normal model using a 26-week cut-point of observed KM data in each treatment group in KEYNOTE-407.

The ERG

The ERG is unaware of the use of this database in other NICE technology appraisals. The ERG has expressed concerns surrounding the appropriateness of the database in estimating survival, i.e. differences in key patient characteristics, differences in treatment

approach between the US and the UK, the lack of information about line of therapies, type of therapies and performance status of included patients.

The ERG also questioned the rationale behind the company using different cohorts from the SEER database to estimate annual mortality risks for 1-5 years, 6-10 years and 11-13 years after follow-up.

The ERG received clinical expert opinion from three clinicians regarding estimated OS and PFS outcomes to address concerns that the company's approach is too optimistic in terms of OS and PFS. For the pembrolizumab combination group two clinical advisors agreed with the projections of the company's KM/log-logistic model for estimating OS, and the KM/SEER model for the standard care chemotherapy group. A third clinical advisor proposed different OS estimates for the pembrolizumab combination treatment group that would lie between the ERG's log logistic and exponential functions. Based on the OS estimates for the comparator group from this third clinical advisor, the ERG assumed the log logistic function fitted using the KEYNOTE 407 dataset. All three clinical advisors agreed that the company's piece-wise log-normal model produced reasonable PFS estimates at 5 years for the pembrolizumab combination therapy. The ERG noted within its report that all clinical advisors found it very difficult to provide these estimates.

Estimates of OS and PFS based on the varying projections are outlined in the table below:

	Clinical Advisor 1		**Clinical Advisor 2**		**Clinical Advisor 3**	
Overall survival	**5 years**	**10 years**	**5 years**	**10 years**	**5 years**	**10 years**
Pembrolizumab combination	20%	11%	20%	11%	15-20%	5-10%
Standard care	8%	3%	8%	3%	8-10%	5%

Progression-free survival	5 years	10 years	5 years	10 years	5 years	10 years
Pembrolizumab combination	10%	-	10%	-	10%	-
Standard care	3%	-	3%	-	3%	-

In its report, the ERG present analyses on optimistic and pessimistic survival modelling. An optimistic analysis is based on the views of clinical advisors 1 and 2 and a pessimistic view is based on the views of the third clinical advisor. An overview of the ERG's optimistic and pessimistic survival analysis can be seen in the table below;

Model	Optimistic analysis – Exploratory analysis 5a	Pessimistic analysis - Exploratory analysis 5b
OS model - pembrolizumab combination therapy	Company's KM/log logistic model (19-week cut-point)	ERG's log logistic model* (no cut-point)
OS model - SoC chemotherapy	Company's KM/SEER model (19-week cut-point)	ERG's log logistic model* (no cut-point)
PFS model - pembrolizumab combination therapy	Company's piecewise log normal model (26-week cut-point)	Company's piecewise log normal model (26-week cut-point)
PFS model – SoC chemotherapy	Company's piecewise log normal model (26-week cut-point)	Company's piecewise log normal model (26-week cut-point)

**The ERG note that its log logistic model broadly approximates the clinician's (advisor 3) expected OS at 5 years*

The ERG highlighted that using the company's base case piece-wise KM/log-logistic model to inform long term overall survival, results in approximately 9.9% of people receiving pembrolizumab combination having an implicit assumption of being cured after 18 years.

	This is because the hazard ratios (HR) are similar to age-related HR observed in the general public, which appears counterintuitive. A graph showing the projections from modelling used by the company and the ERG (both optimistic and pessimistic modelling) can be seen below; (figure redacted)  **Clinical expert opinion** The NICE technical team received estimates for OS and PFS from a clinical expert, which can be seen in the table below. These estimates tend to broadly agree with estimates from clinical advisors 1 and 2 to the ERG. The clinical expert noted the difficulty in estimating long term OS and PFS.

<table>
<tr><td></td><td>
<table>
<tr><td colspan="4"><u>Clinical advisor 4 (NICE)</u></td></tr>
<tr><td>Overall survival</td><td>5 years</td><td>10 years</td><td>20 years</td></tr>
<tr><td>Pembrolizumab combination</td><td>20%</td><td>11%</td><td>4%</td></tr>
<tr><td>Standard care</td><td>8%</td><td>3%</td><td>0%</td></tr>
<tr><td>Progression-free survival</td><td>5 years</td><td>10 years</td><td></td></tr>
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<tr><td>Standard care</td><td>3%</td><td>0%</td><td>0%</td></tr>
</table>
</td></tr>
<tr><td>Why this issue is important</td><td>The choice of data source and statistical method used to estimate longer term OS impacts considerably upon the ICER. It is important that methods used result in clinically plausible survival probabilities and a valid rationale is given for the choice of any statistical method used.</td></tr>
<tr><td>Technical team judgement before engagement</td><td>The technical team acknowledge that the ERG’s clinical advisors appear to broadly agree with the company’s models used to predict OS and PFS. The team also recognises that the clinical advisors reported difficulty in providing these estimates.

The technical team believe that there is high uncertainty surrounding the long-term extrapolation of OS and agree with the concerns expressed by the ERG regarding the SEER database. The team would like more input on how this uncertainty may be addressed and on the suitability of the SEER database for use in NHS decision-making</td></tr>
</table>

Summary of comments	**The Company** The company state that they believe the SEER database to be appropriate to extrapolate long term survival estimates for both the SoC and intervention arms. They believe that despite the Log-logistic curve providing a reasonable statistical fit and clinically plausible SoC survival, the KM/SEER extrapolation is the most appropriate method for extrapolating long-term outcomes rather than KM/Log-logistic for both treatment arms. The company has provided an updated model including an amendment allowing treatment arms to select different long-term extrapolation methods independently. They believe that this will aid the committee in decision making and reduce uncertainty regarding this issue. **The ERG** The ERG state that the company's technical engagement response provides no new evidence or analyses regarding the extrapolation of outcomes for both arms of the KEYNOTE-407 trial, and that the ERG concerns surrounding the company's modelling approach remain: • Outcomes are highly uncertain, due to short duration of trial data in the interim analysis. • The SEER database used by the company in its modelling has not been directly used in previous NICE appraisals of lung cancer treatments. In addition, it is unlikely any sizeable proportion of patients in this database received second-line immunotherapy and survival data dating back to 1992 is unlikely to reflect current practice in the NHS. The SEER database appropriateness is further limited by differences in patient demographics, treatment pathways and healthcare systems between the US and England. • While two of the ERG's clinical advisors believed that the company's use of SEER data may be reasonable for estimating outcomes in the SoC arm, they noted that caution should be exercised due to the differences listed.

	• The use of a relative risk ratio to inform treatment effect is not appropriate as it relates only to a time-specific interval, use of a HR would be more suitable as it accounts for the time at which an event occurs. • The ERG's comparison of observed OS from KEYNOTE-407 and predicted OS from the company's KM/SEER modelling approach (including the relative risk ratio from KEYNOTE-407) suggests that the company's model overestimates the benefits of pembrolizumab combination therapy after 12 months. • The ERG does not believe that there is enough clinical rationale to support the use of piecewise modelling for PFS or OS. The ERG's parametric survival models fitted to the whole KEYNOTE-407 dataset produced estimates of long-term OS for the SoC chemotherapy group which were more plausible than those produced by the company's piecewise models and which were in line with the ERG's clinical advisors' expectations. • All three of the ERG's clinical advisors believed that the company's OS extrapolation for pembrolizumab combination therapy was likely to be optimistic. None of the ERG's experts preferred the company's OS model for pembrolizumab combination therapy. • The ERG notes that the difference between the mean estimates of OS for SoC chemotherapy from the ERG's optimistic and pessimistic scenarios is fairly small (1.97 versus 2.17 years); however, this does impact on the ICER and may influence judgements regarding whether NICE's End of Life (EoL) criteria are met (see issue 7). The ERG also submitted a table (shown below) which can be used to compare estimated survival between the company's model and both ERG models (optimistic and pessimistic) **Pembrolizumab combination therapy – overall survival probability at timepoint**

Time	Company's model (KM/SEER plus relative risk ratio based on months 7-12 of KEYNOTE-407)	ERG's optimistic scenario (company's KM/log logistic model [19-week cut-point])	ERG's pessimistic scenario (ERG's log logistic model [no cut-point])
5 years	0.26	0.20	0.16
10 years	0.16	0.11	0.07
20 years	0.09	0.05	0.03
Standard care chemotherapy – overall survival probability at timepoint			
Time	**Company's model (KM/SEER)**	**ERG's optimistic scenario (KM/SEER)**	**ERG's pessimistic scenario (ERG's log logistic model [no cut-point])**
5 years	0.08	0.08	0.09
10 years	0.03	0.03	0.04
20 years	0.01	0.01	0.01

Clinical expert opinion

During technical engagement, NICE received updated 5-year survival estimates for both the pembrolizumab combination therapy and standard care groups from the clinical advisor previously stated. These updated estimates can be seen in the table below:

Overall survival	5 years	10 years	20 years
Pembrolizumab combination	18%*	11%	4%

	Standard care	9%*	3%	0%
	Progression-free survival	**5 years**	**10 years**	
	Pembrolizumab combination	10%	5%	4%
	Standard care	3%	0%	0%

*Updated estimates

Technical team scientific judgement after engagement	Extrapolation of survival is a key driver of the ICER and the uncertainty around clinical estimates is high. The technical team considers that the SEER database in general is not appropriate for NHS decision making, due to the reasons described in this report. As the company's modelling uses the SEER database in both the intervention and SoC arm, the technical team believe that results from this approach cannot be considered to produce the most plausible ICERs. In addition, the company's application of a relative risk ratio, from months 7-12 in KEYNOTE-407, is not appropriate because it is likely to overestimate the survival benefit of pembrolizumab combination therapy. The survival curves appear to be at their most separated at this timepoint. The technical team prefer the modelling approach of the ERG, which limits the use of the SEER database (optimistic analysis) or removes it fully (pessimistic analysis). The technical team believes that the most plausible survival outcomes are between the ERG's pessimistic and optimistic analysis, while acknowledging high uncertainty around long term outcomes. The ERG's analyses present the high uncertainty in long term outcomes in more detail compared to the company's analyses. The ERG's optimistic analysis uses the KM/SEER extrapolation for the SoC arm and a KM/logistic extrapolation for the intervention arm. The technical team believes that this approach is preferable to the company's modelling as it only uses SEER to inform SoC. It also does not use a relative risk ratio from a specific interval to inform treatment benefit.

	The ERG's pessimistic analysis uses log-logistic extrapolations for both in SoC and intervention arm, and therefore does not use the SEER database to inform outcomes in either arm. Like the ERG optimistic analysis, it does not use a relative risk ratio from a specific interval to inform treatment benefit. Therefore, the ERG's pessimistic analysis is also preferable to the company's modelling approach (as is the ERG's optimistic analysis). Regarding the likely proportion of people who would likely experience a cure, where their risk of death is similar to that of the age-adjusted general public, the technical team believe that the ERGs modelling estimates (~6% optimistic and ~3% pessimistic) are more reasonable than the company's projected 9.9% after 18 years. Again, this view acknowledges the significant uncertainty for this length of extrapolation.

Issue 2 – Place in the treatment pathway of pembrolizumab combination therapy

This issue was resolved at technical engagement and is addressed in table 4.

Issue 3 – Subsequent treatments

Questions for engagement	9. What percentage of people, who receive first-line standard chemotherapy treatment, would be expected to receive second-line immunotherapy following disease progression? 10. How long would these people be expected to be treated with second-line immunotherapy? 11. Which second-line immunotherapies would be used and in what proportions?
Background/description of issue	**The Company** In its model, the company has based the proportion of patients receiving subsequent treatments in both arms on interim analysis of KEYNOTE-407. This resulted in approximately [redacted] of patients in the intervention group receiving second-line chemotherapy

	and [redacted] of patients in the comparator group receiving second-line immunotherapy (pembrolizumab [redacted] or nivolumab [redacted]), chemotherapy or a combination of both. The company have also estimated the duration of second-line treatments based on the interim data for KEYNOTE-407. **The ERG** Clinical advisors to the ERG noted differences between second-line treatments in KEYNOTE-407 and those available in clinical practice in the NHS, for example; patients who receive first-line platinum-doublet therapy would be unlikely to receive this therapy again. In its report, the ERG notes that, because of the immaturity of data, it is possible that the proportion of patients who receive second-line immunotherapy will increase with additional follow-up data from KEYNOTE-407. The ERG also notes that the effect on the ICER of assuming greater second-line immunotherapy use is unclear, as both increased costs and better health benefits can be expected. The ERG also has concerns that using an interim analysis may underestimate the duration of treatment that patients receive in second-line treatment, and that these uncertainties may be resolved through additional follow-up in KEYNOTE-407.
Why this issue is important	Subsequent treatments likely to be received following standard chemotherapy within the NHS should be accounted for and modelled appropriately. This can have a significant effect on cost-effectiveness estimates as greater health gains can be expected along with increased costs, if the proportion of people assumed to receive subsequent treatments is increased
Technical team judgement before engagement	The technical team would like clinical expert input regarding the likely percentage of patients who receive first-line treatment with standard chemotherapy that would go on to receive subsequent immunotherapy treatment within an NHS setting. In addition, it would be useful

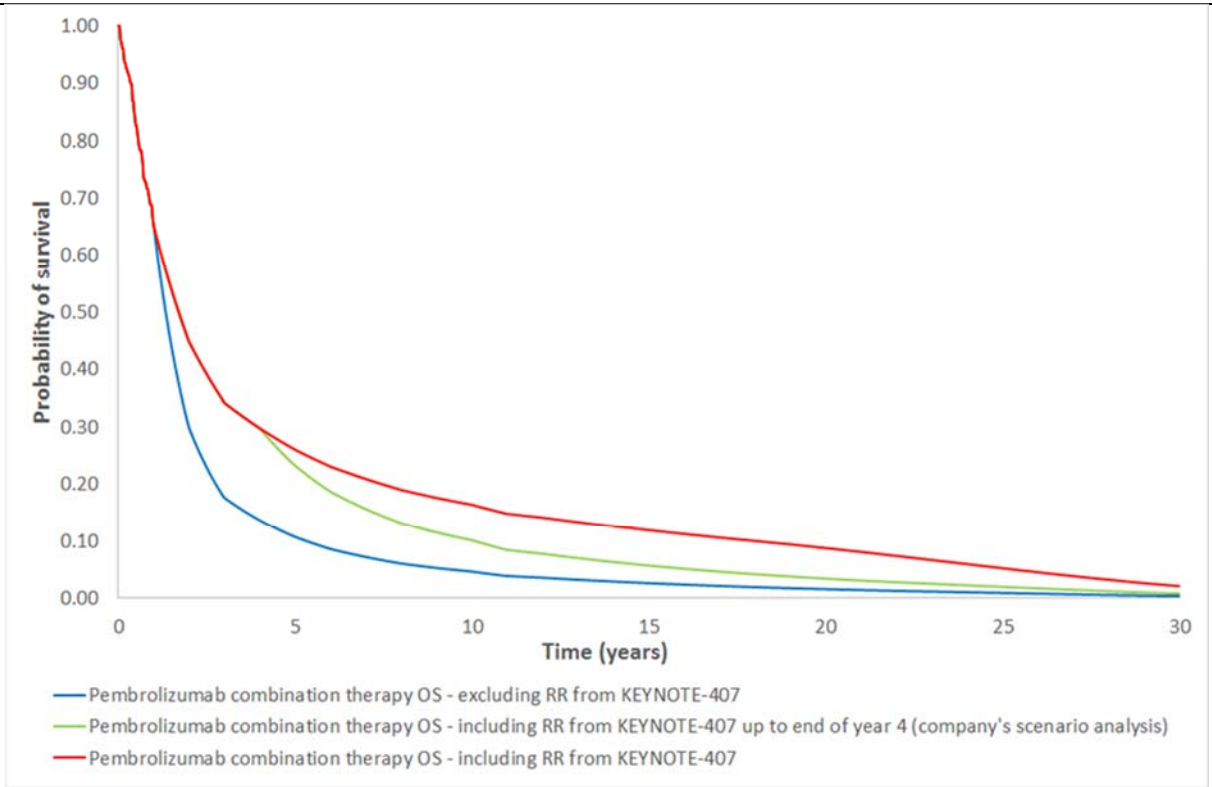
	to obtain clinical expert opinion regarding estimates around time spent on these treatments and the types of immunotherapy likely to be used (with proportions).
Summary of comments	**The Company** Within the available KEYNOTE-407 trial data, [redacted] of patients received second-line immunotherapies following disease progression. During the technical engagement teleconference, clinical experts stated that approximately 50%-60% of people would receive second-line immunotherapies. The company suggest that these estimates are "not vastly different from the proportion observed in KEYNOTE-407 and the cost-effectiveness analysis provided by the company." The company has submitted updated scenario analyses in which they have assumed that 65% of people would receive second-line pembrolizumab monotherapy and 35% of people would receive second-line atezolizumab as per observed clinical practice in NHS England. These estimates were also verified by clinical experts during the technical engagement teleconference. The company has included treatment durations for these second-line immunotherapies from NICE technology appraisal TA 520. **The ERG** The ERG noted that the company's model does not include a causal link between the probability of receiving second-line immunotherapy and OS. As such, increasing the proportion of patients receiving second-line immunotherapy increases the total costs for the comparator group, but has no effect on health outcomes. As a consequence, this improves the ICER for pembrolizumab combination therapy. The ERG believes that the increased use of second-line immunotherapy would improve OS for the SoC chemotherapy group; this improvement is not captured in the analyses. Consequently, the company's revised analyses are likely to favour the pembrolizumab combination therapy group and should be approached with caution.

Technical team scientific judgement after engagement	The technical team considered clinical expert opinion received during the technical engagement teleconference. Based on this, it is appropriate to consider that around 50% of people who progress in the SoC arm of KEYNOTE-407 would receive second-line immunotherapy. The modelling (both by the company and ERG) accounts for the costs of second-line immunotherapies but does not include a causal link between the probability of receiving these second-line immunotherapies and OS; therefore, despite increasing the proportion of second-line immunotherapies, the benefits on OS are not captured. This is likely to underestimate the estimated OS in the SoC arm of KEYNOTE-407, but the magnitude of this is unknown. This should be considered when applying the NICE EoL criteria (see issue 7). Not fully capturing the benefits of second-line immunotherapies is also likely to underestimate the estimates for all ICERs comparing pembrolizumab combination therapy with SoC chemotherapy presented in both the company's and ERG modelling, again the magnitude of this effect is unknown.

Issue 4 – Treatment effect after discontinuation of pembrolizumab treatment

Questions for engagement	12. What is the most clinically plausible assumed treatment effect for pembrolizumab once treatment with this drug has stopped? 13. Is there any additional evidence which could be used to inform the duration of treatment effect?
Background/description of issue	**The Company** The company, within its submission and model, has assumed a lifetime benefit after pembrolizumab combination treatment is stopped, whilst providing no evidence to substantiate this assumption. In its scenario analysis, the company also present results which include a 5-year assumed treatment benefit.

	The ERG As the trial data from KEYNOTE-407 is of short duration, there is high uncertainty around the clinical benefit that occurs once treatment is discontinued. The ERG report does not agree that assuming a lifetime treatment benefit is appropriate, and instead assessed the loss of OS benefits for pembrolizumab combination therapy at 2 years, 3 years and 4 years after treatment discontinuation. The ERG also disagrees with the company's use of a relative risk of death function from the mortality differences between treatment groups observed in months 7-12 within KEYNOTE-407. The ERG presented the effect of using a relative risk ratio indefinitely, excluding it and using it until end of year 4 on survival estimates in the graph below;



The technical team is aware that in previous lung cancer appraisals (e.g. pembrolizumab for PD-L1-positive NSCLC after chemotherapy [TA428] atezolizumab for NSCLC after chemotherapy [TA520]), the committee have preferred to assume a 3-5 year treatment effect duration, commencing after treatment discontinuation (i.e. 3 years after stopping treatment or 5 years from commencing treatment).

Clinical expert opinion

Clinical expert opinion sought by the NICE technical team stated that a treatment effect between 3-5 years seems most plausible.

<table>
<tr><td>Why this issue is important</td><td>The length of assumed treatment benefit after discontinuation impacts upon the ICER, with longer treatment effects associated with a lower ICER (that is, it makes the treatment seem more cost-effective). This is driven by a health benefit being obtained without treatment costs being incurred. It is therefore important to receive clinical expert opinion on this matter, to decide upon which duration of benefit is most appropriate to assume in this population.

The ERG has investigated various treatment effect duration assumptions, which can be seen in the table below;

<table>
<tr><th>Time point after which treatment effect is lost</th><th>Incremental QALYs</th><th>Incremental costs</th><th>ICER</th></tr>
<tr><td>Company's base case (lifetime effect)</td><td>1.68</td><td>£48,278</td><td>£28,672</td></tr>
<tr><td>2 years</td><td>0.76</td><td>£40,010</td><td>£52,425</td></tr>
<tr><td>3 years</td><td>1.04</td><td>£42,414</td><td>£40,947</td></tr>
<tr><td>4 years</td><td>1.15</td><td>£43,444</td><td>£37,730</td></tr>
</table>
QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio</td></tr>
<tr><td>Technical team judgement before engagement</td><td>Lack of mature OS data means there is substantial uncertainty about the duration of pembrolizumab combination treatment effect. The technical team considers that a life time duration assumption is not appropriate because there is a lack of evidence to support this. It is preferable to model a more conservative duration of 3 to 5 years (in line with previous appraisals in this disease area).</td></tr>
<tr><td>Summary of comments</td><td>The Company

The company have submitted updated scenario analysis in which treatment effect ceasing at 5 years post pembrolizumab combination initiation and an analysis in which treatment effect ceases 3 years after treatment discontinuation.</td></tr>
</table>

	The ERG The ERG state that the company has not presented any new evidence relating to the duration over which the treatment effect may apply; this remains a key area of uncertainty. The ERG highlights the following regarding the company's modelling of treatment effects: • The ERG's clinical advisors agreed that a lifetime treatment effect to be overly optimistic. • Removing the treatment effect at earlier timepoints has the propensity to substantially increase the ICER for pembrolizumab combination therapy). • The ERG's clinical advisors noted considerable uncertainty relating to the duration of treatment response and its impact on OS outcomes. As the ERG's modelling approach is based on parametric models that best match clinical expert opinion on long-term survival outcomes, there is no explicit treatment effect in either the optimistic or pessimistic models. The HR varies over time in the ERG's models.
Technical team scientific judgement after engagement	The company's base case, where they have applied a lifetime treatment effect based on the SEER database and the relative risk ratio observed in month 7-12 in the KEYNOTE trial, is viewed by the technical team as not appropriate (see issue 1). Assuming a treatment benefit of 3-5 years is more appropriate than a lifetime treatment effect informed by relative-risk. However, as is stated in issue 1, the technical team prefer the ERG models which either use SEER in only the SoC arm (ERG optimistic model) or do not use SEER in either arm (ERG pessimistic model). The ERG models (optimistic and pessimistic) do not include an implicit treatment effect in the intervention arm as they have used parametric functions validated by clinical expert opinion on most plausible survival outcomes for this group.

Issue 5– Network meta-analysis (NMA) for comparators

This issue was resolved at technical engagement and is addressed in table 4.

Issue 6 – Health related quality of life measurement

Questions for engagement	14. Are time to death utilities appropriate to capture health-related quality of life (HRQoL) within this population? Would health utilities based on progression status be more suited for use? 15. How robust are the health utilities estimates directly collected within KEYNOTE 407? Should utility values from the literature be used instead of utilities collected within KEYNOTE 407? How valid are the utility values used by the ERG in its analyses (from Khan et al)?
Background/description of issue	**The Company** In the company's base case, time to death utility values are used. Their rationale for using this approach is that it provides a better a better HRQoL fit as it considers more health states than a model using health states based on progression status. The company also presented a scenario analysis in which they used directly collected EQ-5D-3L utilities from within the KEYNOTE-407 trial. **The ERG** The ERG expressed concerns over the use of time to death utilities. They note that estimated utility values for the two least severe time to death health states may be overestimated, as these values are similar to the sex-adjusted general population utility values for people aged 65-74 (based on Ara and Brazier study; ERG report pg 120).

	Regarding the company's scenario analysis, which used health states based on disease progression status, the ERG also report concerns over how EQ-5D-3L utilities were collected in the KEYNOTE trial. Within the company submission, EQ-5D-3L questionnaires were administered shortly after disease progression. This may therefore bias mean estimates for health states as data is collected early in each state, which could overestimate the health utility values as HRQoL is expected to decrease with time and following disease progression. The ERG presented alternative analyses using health states based on disease progression status and using EQ-5D-3L utilities taken from the literature in this disease area. Khan et al (which was based on the TOPICAL trial) was the ERG's preferred post-progression health utility source, which reported a utility value of 0.58 for this group. This value was taken from the placebo group within the TOPICAL trial. The ERG a progression-free utility value of [redacted] which is taken directly from the KEYNOTE 407 trial. The technical team are aware that health utilities are allocated to patients based on their disease status (progression free/progressed disease for example) in the majority of appraisals in this area. The team also note that committees have considered a combined approach (using both TTD and progression-status based utilities) in previous pembrolizumab appraisals (TA531 and TA577).
Why this issue is important	Using different methods to capture changes in HRQoL results in different cost-effectiveness results. It is important that the method selected has good clinical rationale as to why it was chosen for use.
Technical team judgement before engagement	The technical team prefer the ERG's approach for modelling HRQoL, which used health states based on progression status sourced from the literature. This approach accounts for the expected negative impact on HRQoL that is expected when patients move from a status of progression free to a progressed disease state and overcomes the issues of overestimation of mean health state utilities directly collected in KEYNOTE-407.
Summary of comments	**The Company**

	The company considers that the time to death (TTD) utility approach allows a better reflection of the HRQoL experienced by patients. They also state that NICE has previously accepted this approach in other technology appraisals (TA402, TA531 and ID1210). The company believes that the utilities reported in KEYNOTE-407 for patients in the TTD states of >360 days and 180-360 days are not implausible (comparable to sex-adjusted general population utility value for individuals 65-74 years old) as cancer patients have been reported to value health states higher than the general population. The company do not consider the utility values from Khan et al to be representative of the population in KEYNOTE-407 due to the population in the TOPICAL study (used in Khan et al) being unsuitable for chemotherapy and less well that the population in KEYNOTE-407. They therefore state that the utility values reported in Khan el al would be significantly lower than that observed in KEYNOTE-407 and not aligned with the patient population. **The ERG** The ERG noted that the company's technical engagement response does not provide any new evidence which justifies their use of the TTD utility approach using data from KEYNOTE-407. The ERG notes the following key points: • EQ-5D data was collected shortly after disease progression in KEYNOTE-407 (at most, 30 days later). As such, the data from KEYNOTE-407 are likely to be subject to informative censoring. Irrespective of whether a TTD approach or progression-based utility approach is taken, the estimates obtained from this data source are likely to be biased and neither method can resolve this problem without the use of external data. • The TOPICAL trial (Khan et al) represents a reasonable alternative source of post-progression utility because: (i) this trial included collection of HRQoL data in progressed patients; (ii) HRQoL was measured using the EQ-5D, and (iii) few

	patients in the placebo group received active therapy after disease progression, hence the estimate is unlikely to be contaminated by post-progression treatments. • The ERG notes that using Khan et al is also in line with the NICE Reference Case and this source has been used to inform post-progression utility estimates in previous NICE appraisals (e.g. TA411 - necitumumab for NSCLC). • The parameter required for the model (EQ-5D utility in patients with progressed disease) does not relate to the randomised populations of these studies. • The company's technical engagement response does not provide any evidence to support their justification of high utility values within their time-to-death approach and the ERG believes that this viewpoint is neither logically consistent or reasonable.
Technical team scientific judgement after engagement	TTD utilities do not appear appropriate for use within this appraisal. The technical team note that the company did not provide any evidence for their statement which says that cancer patients have been reported to value health states higher than the general population. It is preferable to use the ERG's approach for modelling HRQoL, i.e. health states based on progression status. In addition, it is also preferable to use a post-progression utility value from the Khan et al paper, rather than the post-progression utility collected in KEYNOTE-407. This is due to data being collected early after disease progression which will likely overestimate health utility values as HRQoL is expected to decrease with time and following disease progression. The technical team agrees with the ERG's rationale for the selection of a post-progression utility value, as once progressed, patients can be assumed to be more reflective of post-progression KEYNOTE-407 patients. While this approach is not without its limitations, it is preferable to using EQ-5D data collected in the KEYNOTE-407 trial for the progressed group.

Issue 7– End of life considerations

Questions for engagement	16. Under standard care, is the life expectancy of adults with metastatic squamous non-small-cell lung cancer (NSCLC) more than 24 months? 17. Does pembrolizumab combination therapy extend life for more than 3 months compared with standard care?
Background/description of issue	NICE states that for technologies to be considered against its end of life criteria if it meets certain conditions, namely; • The treatment is indicated for patients with a short life expectancy, normally less than 24 months and; • There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. The ERG notes that owing to the short follow-up in the KEYNOTE-407 trial, and the potential benefits of second-line immunotherapy in the standard of care chemotherapy group, the expected survival duration for patients receiving pembrolizumab combination therapy and standard care is subject to considerable uncertainty. The ERG corrected errors in the company's base case results and reported a median estimated survival of 1.97 years in the standard of care arm. This result also appears in the ERG preferred optimistic analysis. When the ERG applied its preferred pessimistic analysis, pembrolizumab combination therapy meets the life extension criterion, but does not meet the 24-month expected survival criterion (standard care arm increased to 2.17 years), meaning that it would not meet NICE's EoL criteria. In both the ERG's preferred optimistic and pessimistic analysis, the extension to life estimate is greater than 3 months. The ERG presented a range of scenario analyses using various parametric models. These analyses show that the EoL criteria is met in the majority of scenarios, however the ICER for pembrolizumab combination therapy is estimated to be above £50,000 for these scenarios.
Why this issue is important	The appraisal committee's judgements about the acceptability of the technology as an effective use of NHS resources will take into account whether the technology meets the

	criteria for special consideration as a 'life-extending treatment at the end of life'. A technology which meets NICE's end of life criteria has an increased maximum acceptable ICER.
Technical team judgement before engagement	The technical team notes that in the most optimistic scenario (company's corrected base case and ERG's preferred optimistic analysis) the technology meets the NICE EoL criteria. However, this is the only scenario in which the EoL criteria is met and the estimated ICER is below £50,000. The technical team also believes that estimates of overall survival in the comparator arm of the KEYNOTE-407 are likely to be overestimated based on the company's model. Therefore, on balance, the technical team considers that it is unlikely that the EoL criteria have been met.
Summary of comments	**The Company** In its response, the company stated that, under standard care, the life expectancy of adults with metastatic squamous NSCLC is less than 24 months due to the clinical characteristics of the population and the limited treatment options for this group. The company also believe that pembrolizumab combination therapy extends life for more than 3 months compared with standard care. This is based on data from the KEYNOTE-407 trial and results from the company's modelling approach. The company therefore believes that pembrolizumab combination therapy meets the EoL criteria. **The ERG** The ERG has stated that there is uncertainty regarding whether the EoL criteria are met. Under the ERG's preferred optimistic scenario, the criteria were met, whilst under the ERG's preferred pessimistic scenario, the criteria were not met. The ERG believes that owing to the uncertainty regarding the expected survival duration for patients receiving SoC chemotherapy (with a proportion of patients also receiving second-line immunotherapy), it is unclear whether pembrolizumab combination therapy meets NICE's EoL criteria. The ERG's exploratory analyses indicate that across the full range of ERG-fitted OS models, the EoL

	criteria are met in the majority of scenarios; however, the ICER for pembrolizumab combination therapy remains above £50,000 per QALY gained across all of these scenarios. With respect to the company's technical engagement response, the ERG notes the following additional observations: • The company's response states: *"The company submitted model predicts a median OS for the SoC arm of 11.5 months using the company's preferred KM/SEER extrapolation. This suggests that the prediction of the model is broadly in line with the observed data."* The ERG notes that this is unsurprising as the observed KM curves are used for the first 12 months of the model. • The company's response highlights that the NICE technical report suggests that OS for the SoC chemotherapy group is likely to have been overestimated using SEER. The ERG believes that it is more likely that OS is underestimated in this group (due to the absence of second-line immunotherapy). • The company's response reports median OS estimates from other trials in patients with NSCLC. The ERG believes that the consideration of median survival is not appropriate for determining average life expectancy. In instances in which treatments are expected to lead to long-term survival in a proportion of patients, median and mean values will diverge. • The company's response states *"it should be considered that approximately 50% of the patients who are treated with first line treatment are actually receiving a second line treatment therefore looking the actual survival of patients with squamous population is expected to be much lower than 24 months."* The ERG notes that second-line immunotherapy use is part of the standard pathway for NSCLC and should be included in any estimates of expected survival for these patients.
Technical team scientific judgement after engagement	The technical team considered the life expectancy of the patient group receiving SoC chemotherapy. As the modelling (both company and ERG) does not explicitly account for second-line immunotherapy survival gains in the SoC arm, the technical team and the ERG believe that

	life expectancy for the SoC arm is underestimated, but it is not known by how much. Therefore, the technical team consider that there is high uncertainty around the life expectancy of the patient group receiving SoC chemotherapy, but it is likely to be over 24 months as in the company and ERG's optimistic modelling the estimate is 1.97 years without accounting for the benefits of second-line immunotherapy treatment (see issue 3). The technical team considered the extension to life of the patient group receiving pembrolizumab combination therapy. The company's model and both ERG optimistic and pessimistic models estimate that the extension to life is over 3 months when comparing pembrolizumab combination therapy to current standard NHS treatment. Therefore, the technical team believe that there is sufficient evidence to indicate that the treatment offers an extension to life of at least an additional 3 months, compared to current NHS treatments. On balance, the technical team believe that pembrolizumab combination therapy does not meet NICE's EoL criteria as there is uncertainty around the short life expectancy criteria (under 24 months). Consideration of the EoL criteria by PD-L1 TPS subgroup (PD-L1 <1%, 1-49% and ≥50%) is discussed in Issue 9.

Issue 8 – Cancer Drugs Fund (CDF)

Questions for engagement	18. Is there further data being collected that could reduce uncertainty surrounding longer term effectiveness and health outcomes in this population? 19. When will these additional data become available? 20. How suitable is the technology for use in the Cancer Drugs Fund (CDF)?
Background/description of issue	The duration of clinical trial data presented within the company's submission is short, leading to considerable uncertainty regarding longer term effectiveness. One of the key uncertainties of the KEYNOTE-407 trial is the survival outcome in the comparator arm, particularly when patients receive second-line pembrolizumab following disease

	progression. Longer term data would assist in more robust overall survival estimates. Long term evidence regarding adverse events, particularly after treatment discontinuation of pembrolizumab combination therapy, is uncertain. Further data collection could help provide more certainty around the safety profile of this indication. The KEYNOTE-407 trial is currently ongoing.
Why this issue is important	The CDF is a potential option if there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies. This means the CDF will fund the drug, to avoid delaying patient access, but would require further information on its effectiveness before it can be considered for routine commissioning when the guidance is reviewed.
Technical team judgement before engagement	The technical team is aware of the high level of uncertainty resulting from the immature data presented from the KEYNOTE-407 trial and that overall survival estimates impact substantially on the ICER. The technical team would like input from the company regarding the timescale of when further data from KEYNOTE-407 is likely to become available, what this additional data will be, and whether any uncertainty around the company's assumed lifetime treatment effect can be resolved. Therefore, the drug may be a candidate for the CDF, but there is uncertainty regarding its suitability.
Summary of comments	**The Company** In its response, the company stated that, "Data from the final analysis of KEYNOTE-407 is expected to be available in [redacted]" The company considers the technology to be suitable for the cancer drugs fund as additional data collection is planned within the KEYNOTE-407 trial which could potentially reduce some of the uncertainties highlighted in the technical report. **The ERG** The company's technical engagement response notes that the final analysis of KEYNOTE-407 is expected in [redacted] The ERG believes that these additional data from KEYNOTE-407 will help to resolve uncertainty surrounding long-term PFS and OS estimates.

Technical team scientific judgement after engagement	At the current value proposition, pembrolizumab combination therapy does not appear to have plausible potential for cost-effectiveness with ICERs all above the £20,000–£30,000 per QALY gained range when commercial arrangements are considered. It is therefore unlikely to meet the criteria for inclusion in the Cancer Drugs Fund. The available KEYNOTE-407 data is immature. If there was a plausible potential for the technology to be cost-effective, further data from KEYNOTE-407 trial may help to reduce uncertainty regarding overall survival extrapolation (Issue 1), treatment effect of pembrolizumab combination therapy (Issue 4) and potential adverse events.

Issue 9 – Subgroup analyses (new)

Background/description of issue	The company and the ERG present subgroup analyses for each PD-L1 expression type (PD-L1 <1%, 1-49% and ≥50%). These analyses include ICER estimates along with modelled life expectancy of SoC and incremental life years gained from pembrolizumab combination therapy by each subgroup. The analyses show that these outcomes vary by PD-L1 subgroup. The treatment pathway for untreated squamous NSCLC differs depending on PD-L1 TPS. For people whose tumours express PD-L1 TPS <1% or 1-49%, standard chemotherapy is offered (as in KEYNOTE-407). For those whose tumours express PD-L1 ≥50%, pembrolizumab monotherapy is recommended (TA531). The comparators used in KEYNOTE-407 does not reflect current NHS clinical practice for PD-L1 TPS ≥50% (see table 3). Therefore, an indirect treatment comparison (ITC) for pembrolizumab combination therapy versus pembrolizumab monotherapy is used to account for this. The ERG has concerns regarding the robustness of this ITC, including uncertainty of where the company sourced the time to treatment discontinuation for pembrolizumab monotherapy.

<table>
<tr><td></td><td>Results in terms of life years gained in the SoC arm and incremental life years gained in the intervention arm can be seen in the table below.

<table>
<tr><th>PD-L1 TPS</th><th>Analysis</th><th>Life years gained-SoC arm (mean)</th><th>Incremental life years gained in intervention arm (mean)</th></tr>
<tr><td rowspan="3"><1%</td><td>Company base case</td><td>1.66</td><td>2.30</td></tr>
<tr><td>ERG optimistic</td><td>1.97</td><td>1.98</td></tr>
<tr><td>ERG pessimistic</td><td>1.40</td><td>1.88</td></tr>
<tr><td rowspan="3">1-49%</td><td>Company base case</td><td>1.80</td><td>2.26</td></tr>
<tr><td>ERG optimistic</td><td>2.02</td><td>1.59</td></tr>
<tr><td>ERG pessimistic</td><td>2.09</td><td>1.03</td></tr>
<tr><td rowspan="3">≥ 50%</td><td>Company base case</td><td>4.55</td><td>-0.65</td></tr>
<tr><td>ERG optimistic</td><td>2.00</td><td>2.02</td></tr>
<tr><td>ERG pessimistic</td><td>4.01</td><td>-(Dominated)</td></tr>
</table></td></tr>
<tr><td>Why this issue is important</td><td>If pembrolizumab combination therapy is not considered cost-effective at the acceptable threshold range for the full untreated squamous NSCLC population, then it may still have the potential to be considered cost-effective for certain PD-L1 TPS subgroups. Subgroup analysis is particularly important as one subgroup (PD-L1 ≥50%) receive a different treatment in the first-line setting. Modelled incremental effectiveness of pembrolizumab combination therapy and life expectancy in the SoC by can be expected to vary by PD-L1 TPS subgroups. Therefore, subgroup analyses should be considered when applying NICE’s EoL criteria and in selection of most relevant ICER estimates.</td></tr>
<tr><td>Technical team judgement after engagement</td><td>Following discussion and review of the evidence regarding subgroups, the technical team considers that subgroup analysis is an important part of decision-making around cost-effectiveness and NICE’s EoL criteria (with issue 3 also considered).

It is unlikely that the EoL criteria are met in the PD-L1 ≥50% subgroup, as estimates for life expectancy in the SoC arm are approximately 2 years and above. There is also uncertainty</td></tr>
</table>

	around effectiveness of the intervention versus pembrolizumab monotherapy. NICE's EoL criteria may be considered for the PD-L1 <1% and PD-L1 1-49% subgroups. It is likely that the PD-L1 <1% subgroup meets the EoL criteria. However, these considerations should also take issue 3 (subsequent treatments in SoC arm) into account. The technical team also notes that analyses using subgroups adds to the considerable uncertainty surrounding long term outcomes for pembrolizumab combination therapy.

3. Other issues for information

Tables 1 to 4 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

The company's updated base-case includes the following:

- Corrected errors
- Removing nivolumab from second-line treatment modelling, as it is currently in the CDF
- Updated proportions on second-line immunotherapies and type of immunotherapy
- Inclusion of disease management costs based on progression status

Table 1 outlines the cumulative effect of all NICE technical team preferred assumptions on the cost-effectiveness estimate.

Alteration	Technical team rationale	ICER	Change from base case
Company updated base case	–	£25,828	
Company updated base case with: • KEYNOTE-407 progression-based utilities • 3-year treatment effect post treatment discontinuation	Removal of time-to-death utilities and the lifetime treatment effect (see issues 4 and 6)	£35,839	+£10,011
Updated ERG preferred optimistic analyses with: • Company's KM/SEER extrapolation for SoC group survival estimates • Log-Logistic extrapolation for intervention group survival estimates	Technical team agree with how the ERG have modelled the uncertainty around survival outcomes (optimistic and pessimistic-see issue 1)	£33,631	+£7,809

• Progression-based HRQoL, with a post-progression utility value from Khan et al • Disease management based on progression status • Updated second-line treatment proportions and durations	and the approach for modelling HRQoL (see issue 6)		
Updated ERG preferred pessimistic analysis with: • Log-Logistic extrapolation for SoC and intervention group survival estimates • Progression-based HRQoL, with a post-progression utility value from Khan et al • Disease management based on progression status • Updated second-line treatment proportions and durations	Technical team agree with how the ERG have modelled the uncertainty around survival outcomes (optimistic and pessimistic – see issue 1) and the approach for modelling HRQoL (see issue 6)	£45,680	+£19,852
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	£33,631* to £45,680*	-

**Technical team believe that the most plausible ICER is higher than the lowest value in the range (£33,681) and could be higher than the highest value (£45,680) in the range. This is because second-line immunotherapy benefits are not fully captured in the modelling for the SoC group. This likely underestimates the ICERs in the technical team's preferred ICER range.*

Table 2 – Subgroups by PD-L1 TPS expressions (Results of ERG-preferred analyses with/without change in second-line treatment regimens (see issue 3), pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel or pembrolizumab monotherapy)

Option	ERG's optimistic scenario							ERG's pessimistic scenario						
	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS ≥50% subgroup														
ERG exploratory analysis 6 - ERG preferred analysis (original)														
Pembrolizumab combination	4.02	2.11	£64,708	2.02	0.91	£35,519	**£39,193**	3.72	2.01	£63,425	-	-	-	**Dominated**
Pembrolizumab mono	3.85	2.06	£67,519	-	-	-	**Dominated**	3.56	1.96	£66,382	-	-	-	**Dominated**
SoC chemotherapy	2.00	1.20	£29,189	-	-	-	-	4.01	2.03	£38,907	-	-	-	**Dominating**
ERG exploratory analysis 6 - ERG preferred analysis, including change in second-line treatment														
Pembrolizumab combination	4.02	2.11	£64,708	2.02	0.91	£33,269	**£36,592**	3.72	2.01	£63,425	-	-	-	**Dominated**
Pembrolizumab mono	3.85	2.04	£67,519	-	-	-	**Dominated**	3.56	1.94	£66,382	-	-	-	**Dominated**
SoC chemotherapy	2.00	1.20	£31,438	-	-	-	-	4.01	2.02	£41,233	-	-	-	**Dominating**
PD-L1 TPS 1-49% subgroup														
ERG exploratory analysis 6 - ERG preferred analysis (original)														
Pembrolizumab combination	3.60	2.13	£69,348	1.59	0.96	£39,146	**£40,767**	3.12	1.91	£67,684	1.03	0.70	£37,023	**£52,680**
SoC chemotherapy	2.02	1.17	£30,203	-	-	-	-	2.09	1.21	£30,661	-	-	-	**-**
ERG exploratory analysis 6 - ERG preferred analysis, including change in second-line treatment														
Pembrolizumab combination	3.60	2.13	£69,348	1.59	0.96	£36,879	**£38,244**	3.12	1.91	£67,684	1.03	0.71	£34,753	**£49,149**
SoC chemotherapy	2.02	1.16	£32,469	-	-	-	**-**	2.09	1.20	£32,931	-	-	-	**-**
PD-L1 TPS <1% subgroup														
ERG exploratory analysis 6 - ERG preferred analysis (original)														
Pembrolizumab combination	3.83	2.03	£64,296	1.98	0.93	£32,126	**£34,392**	3.29	1.85	£61,898	1.88	0.93	£31,918	**£34,239**
SC chemotherapy	1.84	1.10	£32,170	-	-	-	-	1.40	0.92	£29,980	-	-	-	-
ERG exploratory analysis 6 - ERG preferred analysis, including change in second-line treatment														
Pembrolizumab combination	3.94	2.03	£64,296	1.98	0.94	£30,316	**£32,343**	3.29	1.85	£61,898	1.88	0.93	£30,125	**£32,245**
SC chemotherapy	1.97	1.10	£33,980	-	-	-	**-**	1.40	0.92	£31,772	-	-	-	**-**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

** undiscounted; all patients receive only nivolumab (in the original model) or atezolizumab (in the revised model), since pembrolizumab is only available as second-line for patients PD-L1 TPS>1%.*

Table 3: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Second-line immunotherapy benefits in SoC arm	The modelling (both by the company and ERG) accounts for the costs of second-line treatments but does not capture second-line survival gains.	ICERs likely underestimated in all modelled estimates
Long term adverse events of pembrolizumab combination therapy.	If pembrolizumab combination therapy has more adverse events than standard care treatments for this indication, then this results in a reduction in health benefits observed in the intervention arm of the trial.	Unknown – however, if pembrolizumab was shown to cause more adverse events (perhaps through a longer-term follow-up) than comparators, then this will likely increase the ICER.
Immature evidence base	The interim analysis from KEYNOTE-407 is of short duration. Median overall survival in the trial has not yet been reached in all subgroups.	Unknown.
KEYNOTE 407 trial does not reflect current standard care practice within the NHS for people with strong PD-L1 expression >50%	Within the KEYNOTE-407 trial, all patients within the comparator arm are given carboplatin with paclitaxel or nab-paclitaxel. This is not standard care within the NHS for people with a PD-L1 expression of ≥50%, as this group would routinely be given pembrolizumab monotherapy. Therefore, a direct comparison between the intervention and pembrolizumab monotherapy cannot be made.	Unknown. Uncertainty around cost-effectiveness estimates as an indirect comparison is used.

Table 4: Other issues for information

Issue	Comments
Place in the treatment pathway of pembrolizumab combination therapy	Resolved during technical engagement as clinical expert opinion stated that pembrolizumab combination therapy would be used, if approved by NICE, as first-line treatment for people with a PD-L1 TPS <50% and potentially in people with a PD-L1 TPS ≥50% e.g. those with bulky disease.
Network meta-analysis (NMA) for comparators	During the technical engagement teleconference, it was agreed that for the PD-L1 TPS <50% subgroup, the NMA is not required as carboplatin with paclitaxel/nab-paclitaxel can be considered to be broadly equivalent to platinum-based chemotherapies. Therefore, for this subgroup, this issue is resolved. For the PD-L1 ≥50% subgroup, the NMA is needed because pembrolizumab monotherapy was not included as first-line treatment in the KEYNOTE-407 trial.
Stopping rule	The company's submission states that treatment should continue until disease progression or unacceptable toxicity, or for a maximum of 24 months (consistent with the 35-cycle maximum for trial protocol). The NICE technical team note that this is in line with previous pembrolizumab appraisals (TA531 and TA577). The NICE technical team also notes that only a small proportion of patients [redacted] in the intervention arm of KEYNOTE 407 remained on pembrolizumab combination treatment at interim analysis cut-off point [redacted]
Innovation	The technical team believe that all relevant benefits associated with pembrolizumab combination therapy are adequately captured in the model.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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Technical engagement response form

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]

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 **15 March 2019.**

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 any information that is submitted under 'commercial arrangements' 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

MSD have responded to each of the issues raised by NICE below and in addition to this, have provided updated cost effectiveness analysis in the Technical Engagement Evidence Supporting Document (Table 1- Scenario Analyses for the overall population – Comparison versus Standard of Care (SoC) and equivalent in Table 2- Scenario analyses for the subgroup with PD-L1 expression ≥50% - Comparison versus pembrolizumab monotherapy) to aid the committee in decision making. The model includes the following amends and options:

Amends to all Scenario Analyses(S.A) are presented in the supporting document (Table 1- Scenario Analyses for the overall population – Comparison versus Standard of Care (SoC) and equivalent in Table 2- Scenario analyses for the subgroup with PD-L1 expression ≥50% - Comparison versus pembrolizumab monotherapy throughout S.A 1 and 2):

1. Corrected several minor errors pointed out by NICE previously, which include management costs calculation and % time-to-death in the <Cohort Simulation> tab and NMA OS constant HR at the <Parameters tab>.

2. Removed Nivolumab from second line treatment as it is currently available only in the CDF and amended the share of pembrolizumab and atezolizumab in second line to 35% and 65% respectively as per the technical engagement call and in response to issue 3 below.

3. Updated the treatment durations for 2L pembrolizumab[1] and atezolizumab[2] from the corresponding NICE submission documents as per the technical engagement call and in response to issue 3 below.

4. Inclusion of disease management costs modelled based on progression status based on the committee preference documented in the technical report.

Options included in various scenario analyses presented in the supporting document (Table 1- Scenario Analyses for the overall population – Comparison versus Standard of Care (SoC) and equivalent in Table 2- Scenario analyses for the subgroup with PD-L1 expression ≥50% - Comparison versus pembrolizumab monotherapy S.A detailed below):

5. Treatment waning applied at 3 years post treatment discontinuation in response to issue 4 discussed below (applied in S.A 1b, 2.b, 1.d and 2.d and equivalent in Table 2 for comparison with pembrolizumab monotherapy in PD-L1 ≥50% subgroup)

6. Progression based utility based on KEYNOTE-407 – not the published paper recommended by the ERG for reasons stated below in response to issue 6 (applied in S.A 1.c, 2.c, 1.d and 2d and equivalent in Table 2 for comparison with pembrolizumab monotherapy in PD-L1 ≥50% subgroup)

7. Allowed different treatment arms to select SEER data option independently for reasons discussed in response to issue 1 (applied in S.A 2a, b, c, d and equivalent in Table 2 for comparison with pembrolizumab monotherapy in PD-L1 ≥50% subgroup)

Issue 1: Extrapolation of overall survival	
How appropriate is the use of the SEER database to extrapolate long term survival?	In the absence of recent published UK data and with traditional extrapolation approaches yielding unrealistic long-term survival estimates for the SoC arm, it was necessary to look to another data source. There is a paucity of data, however this was available for a U.S cohort from the U.S. Surveillance Epidemiology and End Results (SEER) program. SEER database consists of 18 different state registries and encompasses 34.6% of the U,S population[3].Geographic areas are selected for inclusion in the SEER Program based on their ability to operate and maintain a high quality population-based cancer reporting system and for their

	epidemiologically significant population subgroups[4]. These areas are representative of the demographics of the entire U.S. population[3]. Whilst MSD notes, it is not ideal to use a U.S cohort for generalisation to the UK, steps were taken to validate this and obtain as much synergy as possible. • The longest available follow up from SEER were used - Data from 1992-2014 were analysed for metastatic squamous NSCLC patients with data beyond 13 years showing insufficient sample size within SEER for stable reporting of estimates. • As patients within the KEYNOTE-407 trial were an average of 2 months from their date of diagnosis with metastatic squamous NSCLC at baseline, survival within the SEER database was similarly analysed starting from 2 months post-diagnosis. • SEER data from 2010-2014 were utilised to assess survival during years 1-5 of follow-up, data from 2000-2014 for years 6-10 of follow-up and data from 1992-2014 for years 11-13 of follow-up. The ERG noted uncertainty around the rationale for this however the time period from SEER for model years 2-5 was 5 years of data (years 2010-2014), but was longer for years 6-13 due to the need for a longer lookback and larger sample size. The intent was to make use of the most recent data available for each follow-up period. There is a degree of movement in the mortality risks during years 10-13, but not so much to make the data non-useful or unduly influence the modelling.

	• Discussion with clinical experts prior to submission and post submission have broadly agreed with the approach taken by MSD given the paucity UK of data and changing treatment landscape whilst agreeing that there are limitations to the database but that in this context, its use is appropriate. • In a recent NICE TA in this patient population in second line [5], the manufacturer used SEER data to validate OS extrapolations. Although, equivalence between the KEYNOTE-407 and clinical trial utilised in the aforementioned TA (Checkmate-017) cannot be inferred, the patient characteristics and potential outcomes can be considered broadly similar for at least the 52% of the KEYNOTE-407 population who go on to receive a 2L therapy following SoC in the economic model. • The technical report suggests that the NICE technical team also received estimates for OS and PFS from a clinical expert. These estimates tend to broadly agree with estimates from clinical advisors 1 and 2 to the ERG which were in line with the company's use of KM/SEER extrapolation for the SoC arm although slightly lower than the company estimates for pembrolizumab combination.
Would the existing trial data from KEYNOTE 407 be more suitable to use for extrapolation?	As noted in the CS, the existing trial data from KEYNOTE-407 should not be used alone for extrapolation of long term outcomes. As an initial modelling approach, parametric models were fitted to KM full OS dataset to extrapolate outcomes over the model time horizon, details of which can be found in the CS and appendix L. As part of this exercise, in determining what would be the most appropriate parametric extrapolation method, the clinical plausibility of the fittings was investigated.

	The exponential fit was the best statistically but provided clinically implausible SoC survival of ~1% at 5 years which is too low given the advances in care of this patient population in the 2L setting. Clinical advisors to the ERG and NICE have also agreed this. The Log-logistic provides a reasonable, but not the best, statistical fit and a more clinically plausible SoC survival of 11% SoC OS at 5 years. However, the clinical plausibility is based on that provided within the SEER database and clinical opinion and thus it is more relevant to use the actual real-world evidence data (SEER) for extrapolation. Therefore, MSD suggests that the CS KM/SEER extrapolation is the most appropriate method of extrapolation of long term outcomes rather than KM/Log-logistic for both treatment arms. S.A 1.a, b, c and d (and equivalent in Table 2 for comparison with pembrolizumab monotherapy in PD-L1 ≥50% subgroup) therefore utilize the original CS survival analysis plus/minus the points mentioned at the start of this document to assist in reducing uncertainty on the other issues presented here. The technical report and ERG report notes that 2/3 clinical advisors agreed with the projections of the CS KM/SEER extrapolation for the SoC arm in addition to those clinicians consulted by MSD. Therefore, MSD and the ERG are in agreement on this point. However, the ERG also uses a different extrapolation method for the pembrolizumab combination arm to that of the SoC arm based on clinical feedback to suggest the CS estimates are high. MSD notes that this method is not in line with the DSU guidance which states: “Where parametric models are fitted separately to individual treatment arms it is sensible to use the same ‘type’ of model, that is if a Weibull model is fitted to one treatment arm a Weibull should also be fitted to the other treatment arm. This allows a two-

	dimensional treatment effect in that the shape and scale parameters can both differ between 40 treatment arms, but does not allow the modelled survival for each treatment arm to follow drastically different distributions. If different types of model seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis". [6] MSD used the same survival model for both treatment arms in which the clinical experts consulted by the ERG, NICE and the company have agreed with for the SoC arm. As discussed, some clinical advisors suggest that the pembrolizumab combination arm long term estimates may be high. However, a recently published paper also suggests that manufacturer reported estimates for long term OS of IO drugs tend to underestimate the results once longer term data cuts are available if anything [7]. However, to aid the committee in decision making and in line with 2/3 clinical experts consulted on the clinical plausibility of the long term extrapolation of both treatment arms, MSD have provided in the supporting documentation some further analysis including the amend allowing treatment arms to select different long term extrapolation methods independently and thus using one of the ERG preferred approaches of KM/SEER for SoC and KM/Log-logistic for pembrolizumab combination plus/minus the points mentioned at the start of this document to assist in reducing uncertainty on the other issues presented here (S.A 2a, b, c and d Table 1 and equivalent in Table 2 for comparison with pembrolizumab monotherapy in PD-L1 ≥50% subgroup of the supporting document). This choice of long term extrapolation of both arms is most in line with what clinical expert feedback has suggested is plausible despite the different models applied to treatment arms.

Which statistical method is preferable to use in when estimating long term outcomes in this population? Would another parametric function be more appropriate?	As noted above with the rationale for this, the most appropriate method for extrapolation of long term outcomes would be the CS KM/SEER method across both treatment arms. However, S.A have been shown in the supporting document applying different long term survival models to treatment arms in line with clinical feedback to NICE and the ERG.
What proportion of patients in the pembrolizumab combination arm would you expect to be alive at 5 and 10 years? What proportion would you expect to be progression-free at these time points?	Company base case assumes: OS: 25.9% and 16.3% (5 and 10 years respectively) PFS:10.4% and 6.2% (5 and 10 years respectively) As mentioned above, the paper referenced above [7] suggests the manufacturer tends to underestimate OS for IO drugs in a study of recent NICE submissions. S.A 2.a, b c and d (and equivalent in Table 2 for comparison with pembrolizumab monotherapy in PD-L1 ≥50% subgroup) have been provided in supporting documentation to show alternative assumptions in line with NICE and ERG consulted clinical experts.
What proportion of patients in the standard of care arm would you expect to be alive at 5 and 10 years? What proportion would you expect to be progression-free at these time points?	Company base case assumes: OS: 7.8% and 3.4% (5 and 10 years) PFS:2.7% and 1.2% (5 and 10 years)

	Clinical input both to NICE and the company has suggested that the OS assumptions for SoC are broadly in line with reality and that the pembrolizumab combination arm may be high. S.A 2.a, b c and d (and equivalent in Table 2 for comparison with pembrolizumab monotherapy in PD-L1 ≥50% subgroup) have been provided in supporting documentation to show alternative assumptions in line with NICE and ERG consulted clinical experts.
Is treatment with pembrolizumab combination likely to be curative in some people?	Using the CS preferred assumptions, at around 18 years in the pembrolizumab combination arm, the general population mortality cap comes in to place suggesting that for those 9.9% of patients in this arm still alive at this point, their risk of mortality going forwards is equal to that of the general population. MSD have consulted with clinical experts on this point and it has been suggested that if a patient were to survive to 18 years post diagnosis then it would be reasonable to assume their mortality risk was that of the general population and that this could be possible for a proportion of patients.
Issue 2: Place in the treatment pathway of pembrolizumab combination therapy.	
Would it be more appropriate to use pembrolizumab combination therapy as a first line treatment option for patients who do not have strong PD-L1 expression (TPS <1% and 1-49% subgroups), or to reserve immunotherapy as a treatment option at second-line?	Clinicians consulted by the company were strongly supportive of using pembrolizumab combination 1L, due to the loss of patients who are not fit to receive 2L, which was estimated at between 40% and 60% and that generally QoL declines over multiple lines of therapy. In addition, squamous

	NSCLC treatment options have been very limited for decades and the prognosis remains poor[8], hence a 1L IO option with proven efficacy should not be limited to 2L. As per CS we believe that treatment with pembrolizumab combination offers a substantial, clinically meaningful benefit to squamous NSCLC patients regardless of PD-L1 expression as a 1L option. This is shown in the OS and PFS results in the attached evidence document. These results show there is an unmet need for an alternative treatment option in this patient population, particularly for patients with an aggressive disease who progress rapidly or those with a high tumour burden that early progression may lead to functional decline precluding 2L IO treatment, these patients would benefit from a combination therapy (Tables 3 & 4, Figures 1-8). Evidence submitted in Table 5 reiterates the importance of effective 1L treatment for this patient population, rather than to reserve it for 2L. The rationale is due to the larger number of patients who discontinued treatment because of progressive disease, adverse event and physician decision who received no further 2L treatment in the control arm compared to the pembrolizumab combination arm. A systematic literature review conducted to identify observational cohort studies, providing real-world context, published between January 2019 and March 2017 looked at the impact of recently approved treatments for advanced NSCLC. Seven retrospective medical record reviews or database analyses and 5 prospective cohorts were included in the qualitative data synthesis. It was described that, in most studies that reported the proportion of patients with advanced NSCLC treated across lines of therapy, between one-third to one-half of those who received 1L treatment also received 2L therapy. Reasons for not receiving later lines of therapy included poor PS and poor

	response to 1L therapy, further highlighting the importance of maximizing the chance of response to 1L treatment [9]
Would it be more appropriate to use pembrolizumab as first-line combination therapy or as monotherapy for patients with PD-L1 strong expression (TPS >50%)?	If pembrolizumab combination is to be approved by NICE in the 1L setting of the metastatic squamous population, published evidence and clinical opinion suggest that it should be made available not only to patients with PD-L1 expression <50% (who currently don't have access to immunotherapy until 2L) but also to those with PD-L1 expression ≥50%, even though pembrolizumab monotherapy is available for this group. While there is no direct comparison of the pembrolizumab combination versus pembrolizumab monotherapy, patients with squamous NSCLC have distinct clinical and epidemiological features which suggest that the action of pembrolizumab combination might be more appropriate at least for a subset of them. Patients with squamous NSCLC are usually heavy smokers, older, present with comorbidities and pronounced symptoms[8]. Additionally, squamous tumours are usually centrally located and as such are more likely to invade larger blood vessels and cause bronchial obstruction[8]. Published evidence suggests that squamous tumours grow more quickly than adenocarcinoma (median doubling time was found to be 160 days for squamous NSCLC compared with 387 days for adenocarcinoma[10]) and clinical opinion suggests that about a quarter of squamous NSCLC patients present with very aggressive disease including significant weight loss, high tumour and symptom burden or "bulky disease". Pembrolizumab monotherapy has been approved previously by NICE as an effective option versus chemotherapy in patients with PD-L1 ≥50%. Clinical opinion suggests that they would

	value the option to give the pembrolizumab combination 1L due to the known delayed effect of IO alone. The option of pembrolizumab combination is also supported in specific cases of patients with PD-L1 ≥50% by The Society for Immunotherapy of Cancer[11] The OS and PFS results of KEYNOTE-407 show the curves on the KM plots separated early for the PD-L1 ≥50% subgroup (Figure 3 and Figure 7). The PFS of the PD-L1 ≥50% subgroup in KEYNOTE-407 was 8.0 months vs. 4.2 months [hazard ratio, 0.37; 95% CI, 0.24 to 0.58] (Figure 7) which suggests that in cases where clinicians need to gain control over aggressive tumours sooner rather than later, the addition of chemotherapy to pembrolizumab can provide substantial benefit. Finally, the need to gain control of the tumours fast is particularly relevant to the UK: according to the most recent report from the NHS, only 72.3% of patients with lung cancer receive their first treatment within the 62 days target after urgent GP referral[12]
Issue 3: Subsequent treatments.	
What percentage of people, who receive first-line standard chemotherapy treatment, would be expected to receive second-line immunotherapy following disease progression?	**Error! Reference source not found.** also highlights, as per the proportions of patients receiving subsequent therapy in the model, that out of those who discontinued therapy (academic/commercial in confidence information removed in the pembrolizumab combination arm and 208 in the control arm), approximately academic/commercial in confidence information removed of patients in the pembrolizumab combination arm were receiving 2L chemotherapy and academic/commercial in confidence information removed in the control arm were receiving any 2L therapy which could have included: 2L IO, chemotherapy or both. These proportions of patients

	who were receiving 2L treatment, discontinued due to progressive disease, adverse event or physician decision. These proportions are in line with clinical expert testimony. **Error! Reference source not found.** highlights that of the remaining 208 participants who discontinued study treatment in the control group, 75 eligible participants who had disease progression verified by BICR crossed over to pembrolizumab monotherapy within the study. An additional 14 participants received a checkpoint inhibitor (pembrolizumab, atezolizumab, or nivolumab) as subsequent therapy outside of the study. A total of academic/commercial in confidence information removed participants in the control group are shown as receiving a subsequent checkpoint inhibitor. However, academic/commercial in confidence information removed participant crossed over to pembrolizumab monotherapy within the study before receiving Atezolizumab outside of the study; therefore, a total of academic/commercial in confidence information removed participants were included in the crossover calculations. Thus, 42.8% (academic/commercial in confidence information removed) of participants in the control who discontinued study treatment crossed over to a checkpoint inhibitor. Clinicians have suggested that it would be around 50%-60% which is not vastly different from the proportion observed in KEYNOTE-407 and the CE analysis provided by the company.

How long would these people be expected to be treated with second-line immunotherapy?	Evidence submitted in Table 7 shows mean duration of treatment for patients who crossed over from the control arm to pembrolizumab monotherapy of academic/commercial in confidence information removed days. NICE suggested during technical engagement that the company provide 2L treatment following SoC to be 65% pembrolizumab monotherapy and 35% atezolizumab as per observed NHSE clinical practice. The 2L IO therapies included in the analysis provided in the supplementary documentation are taken from the pembrolizumab and atezolizumab NICE submissions and are 106 days [2] and 106 days median duration [2]. The distributions and durations of therapies described here have been included in the analysis presented in the supporting document (Table 1 and equivalent in Table 2 for comparison with pembrolizumab monotherapy in PD-L1 ≥50% subgroup throughout all S.A)
Which second-line immunotherapies would be used and in what proportions?	Table 8 Summary of subsequent antineoplastic therapy (Overall population) shows the different IOs subjects received outside of the crossover population. It reports out of the academic/commercial in confidence information removed participants who received second line IO outside the protocol, academic/commercial in confidence information removed received atezolizumab, academic/commercial in confidence information removed received nivolumab and academic/commercial in confidence information removed received pembrolizumab. Since nivolumab is available via the CDF it is not considered a comparator. Therefore, clinicians suggest 65% and 35% receive pembrolizumab and atezolizumab, respectively, in the 2L setting

	reflected in the analysis presented in the supporting document as described above (Table 1 and equivalent in Table 2 for comparison with pembrolizumab monotherapy in PD-L1 ≥50% subgroup throughout all S.A).
Issue 4: Treatment effect after discontinuation of pembrolizumab treatment	
What is the most clinically plausible assumed treatment effect for pembrolizumab once treatment with this drug has stopped?	MSD notes it is unclear what the true effect of pembrolizumab combination would be in the patient population assessed here but also that there is no data to suggest a waning of treatment effect. A recent poster from KEYNOTE-010 (pembrolizumab monotherapy in the second line setting for PD-L1–expressing advanced NSCLC) suggests that most patients who completed 35 cycles or 2 years of pembrolizumab therapy had durable response, with ongoing response in 64% of patients at median follow-up of 43.4 months [13] Additionally, a flattening of the KM curve can be seen around 4years. Additional data in melanoma for patients who completed 2 years of pembrolizumab shows that at 4 years, 28 had complete response, 65 had partial response and 10 had stable disease [14]. Response is ongoing in 56 patients who had partial response. Within those with complete response, 26 patients had an ongoing response and 2 had confirmed progressive disease [14]. However, as per the NICE technical team request, MSD have provided analysis in the supplementary document which includes S.A assessing treatment effect duration ceasing at 5 years post pembrolizumab treatment initiation (Table 1 S.A 1.c, d, 2.c and d and equivalent in Table 2 for comparison with pembrolizumab monotherapy in PD-L1 ≥50% subgroup).

Is there any additional evidence which could be used to inform the duration of treatment effect?	As described above.
Issue 5: Network Meta-analysis (NMA) for comparators	
Do the NMAs and indirect treatment comparisons provide robust enough evidence for decision making? Are the trials included in the NMAs and ITCs generalizable to the UK?	The technical report states that "The ERG has concerns on how the company has carried out their NMA and ITCs. None of the comparator trials in the NMA included the use of second-line immunotherapies." With IO therapy being relatively new to clinical practice in this patient population, the published studies on comparator efficacy pre-date the availability of immunotherapy treatment options, however for the CE analysis for NMA comparators costs for 2L IO as per the KEYNOTE-407 trial comparator were included. The ToT assumed for NMA comparators was equivalent to that of the trial comparator arm which can be justified by a lack of statistical differences in OS/PFS across the comparators. In reality, clinical advisors have pointed out that all of the available current first line options can be considered broadly equivalent. To support this, they referenced a meta-analysis by Treat et al. Therefore, to include 2L IO therapy as per that observed in the KEYNOTE-407 trial as the company has done can also be considered broadly equivalent across options including those in the NMA analysis. Additionally, 2L IO is not SoC in the UK following a first line IO therapy and so this issue should not affect the robustness of the evidence for the ITC versus pembrolizumab monotherapy in PD-L1 ≥50% as the question might suggest.

	As agreed on the technical engagement call, since clinical opinion suggests all comparator treatments currently available in the 1L are comparable, MSD have taken no further action on this point and all analysis provided in the supplementary document are versus the trial comparator for the Overall population (Table 1) and pembrolizumab monotherapy (for PD-L1 ≥50% subgroup) (Table 2).
Should the trials including an ECOG performance status of 2 be excluded or adjusted for to minimise the risk of bias?	It was necessary to include trials that enrolled patients with an ECOG PS of 2 in order to form connected networks of evidence with the relevant comparators. For example, in the pure squamous network for OS, all connections between pembro + carboplatin + pac/nab-pac and other interventions (carb + gem, cis + gem, cis + doc, cis + pac, and carb + pac/nab-pac) are informed by either Saad 2017 (26.8% ECOG PS 2) or ECOG 1594 (5.5% ECOG PS 2). Consequently, the decision was made to exclude only trials in which greater than 50% of patients had an ECOG performance status of 2. This decision was consistent with the KEYNOTE-024 and KEYNOTE-189 submissions to NICE which were accepted by the committee [15],[16]. While this data is limited, there does not seem to be a correlation between the proportion of patients with an ECOG PS of 2 and the treatment effect. This suggests that the imbalance in the distribution of ECOG scores between trials does not bias the NMA. While performance status is clearly a prognostic factor, the difference in the distribution of patients with ECOG PS 2 between trials only matters if performance status is a relative treatment effect modifier for the various comparisons. The Table 9 in the evidence document below shows the HRs for cis + gem vs. carb + gem in the 4 trials comparing these regimens, along with the proportion of

	patients with ECOG PS 2 in the trials. While this data is limited, there does not seem to be a correlation between the proportion of patients with an ECOG PS of 2 and the treatment effect. This suggests that the imbalance in the distribution of ECOG scores between trials does not bias the NMA. As agreed on the technical engagement call, since clinical opinion suggests all comparator treatments currently available in the 1L are comparable, MSD have taken no further action on this point and all analysis provided in the supplementary document are versus the trial comparator for the overall population (Table 1) and pembrolizumab monotherapy (for PD-L1 ≥50% subgroup) (Table 2).
Are the various standard chemotherapy regimens considered to be broadly similar?	As mentioned above clinical advisors have pointed out that all of the available current first line options can be considered broadly equivalent. To support this, they referenced a meta-analysis by Treat et al. As agreed on the technical engagement call, since clinical opinion suggests all comparator treatments currently available in the 1L are comparable, MSD have taken no further action on this point and all analysis provided in the supplementary document are versus the trial comparator for the overall population (Table 1) and pembrolizumab monotherapy (for PD-L1 ≥50% subgroup) (Table 2).
Issue 6: Health related quality of life measurement	

Are time to death utilities appropriate to capture health-related quality of life (HRQoL) within this population? Would health utilities based on progression status be more suited for use?	The time to death (TTD) utility approach allows a better reflection of the HRQoL experienced by patients through time as the quality of life significantly decreases as patients get closer to death. A similar approach was presented in: • NICE TA402: the manufacturer used utility values from the PARAMOUNT trial by treatment arm, progressed state and time to death [17]. • NICE's technology appraisal guidance on pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531) and the committee accepted the TTD approach. [15] • ID1210 for Atezolizumab combination in 1L NSNSCLC in which the ERG commented that "the proximity to death approach has more face validity than pre/post-progression analysis & data from IMpower150 is preferred over values from published literature"[18] The utilities derived from KEYNOTE-407 were identified from the ERG as implausibly high for patients with time to death >360 days and 180-360 days (utility values were 0.796 and 0.762 respectively) since they were high in comparison to the sex-adjusted general population utility value for individuals 65-74 years old (estimated utility=0.799) (Ara and Brazier). The utilities reported in KEYNOTE-407 are not implausible as cancer patients have been reported to value health states higher than the general population which may be related to chronically unwell, individuals having more to gain from an improvement in quality of life. Patients who have regularly

	experienced ill health may perceive their improved health state, or a better hypothetical health state, of greater value. Compared with the general population, cancer patients have consistently reported higher patient values when using a time trade off approach.
How robust are the health utilities estimates directly collected within KEYNOTE 407? Should utility values from the literature be used instead of utilities collected within KEYNOTE 407? How valid are the utility values used by the ERG in its analyses (from Khan et al)?	The NICE reference case specifies that the EQ-5D is the preferred measure of health-related quality of life in adults. Additionally, health-related quality of life, or changes in health-related quality of life, should be measured directly by patients and the valuation of health-related quality of life measured by patients should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method. In the CS, MSD followed the NICE reference case by estimating utilities based on the EQ-5D data collected in KEYNOTE-407, and applied the UK tariff to reflect valuations from the UK general public which is in line with the NICE reference case[19] In addition, MSD do not consider the utility values from Khan et al. to be representative of the population in KEYNOTE-407. The population included in Khan et al. is unsuitable for chemotherapy and significantly less well than the population in KEYNOTE-407 based on the fact that in the TOPICAL trial used in Khan et al, median age was 77 years, 90% of participants had several comorbidities, and less than 2% were given second-line treatment. The population in KEYNOTE-407 is significantly more well with a median age of 65 years, ECOG performance status of 0 or 1 and 27.4% for pembrolizumab + chemotherapy and 51.9% for chemotherapy patients receiving second line treatment.

	KEYNOTE-407 also only included patients with ECOG status 0-1 while in the TOPICAL trial over 80% of the population had ECOG 2 or 3 and those patients with a performance score of 0–1 in TOPICAL had comorbidities - 92% (98 of 106) had CCI scores of ≥3, 95% (101 of 106) had creatinine clearance. Therefore, it is expected that the utility values reported in TOPICAL trial used in the Khan et al would be significantly lower than that observed in KEYNOTE-407 yet not aligned with the patient population. In conclusion, it is known that long-term HRQoL data can be challenging to obtain because PRO completion rates drop off over the course of trials due to adverse events, progression, and death. Following disease progression and discontinuation of treatment or the trial, the feasibility of continuing to administer PRO assessments that are tied to a clinic visit for receipt of study treatment is quite low. In KEYNOTE-407, PRO data were collected post-progression by including an assessment at the 30-day safety follow-up visit, this visit followed treatment discontinuation primarily due to disease progression. While MSD acknowledge the uncertainty that the lack of post progression data brings, utilities elicited from the pivotal trial providing the evidence base for the submission are more relevant. As discussed during the technical engagement call, MSD have presented analysis in the supplementary document using progression based utility from KEYNOTE-407 rather than the published Khan et al values which are heterogenous to the KEYNOTE-407 trial population (Table 1 S.A 1.b and d, 2.b and d and equivalent in Table 2 for comparison with pembrolizumab monotherapy in PD-L1 ≥50% subgroup).

Issue 7: End of life criteria	
Under standard care, is the life expectancy of adults with metastatic squamous non-small-cell lung cancer (NSCLC) more than 24 months?	The prognosis for patients with metastatic lung cancer is typically very poor and the importance of how we treat the disease based on histology has been recognized only in recent years, therefore there is a paucity of squamous-specific real-world data. However, it is widely accepted that life expectancy is low and in squamous NSCLC patients is poorer than those with non-squamous histology and likely to be under 24 months. This is due to the clinical characteristics as well as the limited treatment options for this group. Therapeutic options developed in the last 10 years are not indicated for squamous NSCLC, highlighting the unmet need to these patients who are still treated with palliative chemotherapy in the first line setting which is the same treatment as decades ago. It should be noted that while pembrolizumab monotherapy is available for squamous NSCLC patients with PD-L1≥50%, only about a third to a fourth of squamous patients are falling into this category (28% of patients that were screened from KEYNOTE-001 (n = 1242), KEYNOTE-010 (n = 2699), and KEYNOTE-024 (n = 1938) had PD-L1 ≥50%[20]) and therefore are eligible for first line immunotherapy. The rest of the patients have access to immunotherapy only as a second line treatment with the prognosis being significantly lower in this setting. Efficacy results from KEYNOTE-407 suggest that the median overall survival (OS) of patients who are treated with carboplatin/paclitaxel or nab-paclitaxel is 11.3 months (95% CI, 9.5 to 14.8)[21]. This figure includes patients that crossed over to pembrolizumab and therefore benefited from its treatment effect. (42,8% of the patients who discontinued their treatment with chemotherapy received pembrolizumab[21] and this proportion is close to the 50% of patients estimated to receive

	2L therapy from clinicians). The company submitted model predicts a median OS for the SoC arm of 11.5 months using the company's preferred KM/SEER extrapolation. This suggests that the prediction of the model is broadly in line with the observed data. In addition, all of the additional analysis presented in the supporting document here present a SoC OS of less than 24 months (Table 1 and 2 of the supporting document). The technical report states that SoC OS is likely to be overestimated based on the CS SEER extrapolation which therefore implies it does not meet the less than 24 month life expectancy criteria. If the committee believe that SoC OS is overestimated by the company, then it is more likely on balance that SoC OS is less than 2 years and EoL criteria is met. Given that one of the ERG preferred analysis and the company base case produce a value less than 2 years for SoC, and the other ERG preferred analysis is only 0.17 over 2 years it is more likely that the criteria are met. In another attempt to validate the poor life expectancy in the squamous population, randomized phase III studies were looked in respect of their median OS in the first and second line setting: Socinski et al. reported a median OS in the first line of 9.5 months with nab-paclitaxel and 10.7 with paclitaxel.[22] Schiller et al. reported a median OS of 7.9 months comparing the four platinum based regimens. [23] In the second line setting, recently updated results from the phase III OAK trial [24] suggest that mOS in the second line setting was 8.89 months while in a poster presentation in October 2018, KEYNOTE-010 reported median OS of patients on second line pembrolizumab of 11.8 months [13]. Please note that this figure includes squamous and non squamous patients therefore squamous OS is expected to be lower than that. Also, patients with squamous NSCLC treated with nivolumab had a mOS of 9.23 months based on a 3-year follow up of Checkmate-017.[25]

	Based on the information from the phase III trials provided above the overall survival of the squamous population with the current SoC treatment is not above 24 months even when considering both first and second line treatments. Also, it should be considered that approximately 50% of the patients who are treated with first line treatment are actually receiving a second line treatment therefore looking the actual survival of patients with squamous population is expected to be much lower than 24 months. Real world survival data are available from the National Lung Cancer Audit and suggest 1 year all stage survival 37% and 1 year survival for stage IV only 15.5%[26] This figure includes both squamous and non-squamous patients; the squamous ones tend to be generally a little older with more comorbidities due to nearly all being heavy smokers and often harder to treat as a result. Hence on average they are likely to have OS less than 2 years. MSD also notes that it has been the case in a previous NICE TA in metastatic HER2+ breast cancer for pertuzumab TA509) in which the committee considered it reasonable to apply flexibility in its interpretation of the EoL criteria (which specifies that life expectancy of patients would be normally less than 24 months) for exceptional circumstances[27]. In that specific case: • the OS without the new drug exceeded 24 months and • the new drug provided significant extension to life beyond 3 months • the new drug is combined with existing treatment

	• and both the existing treatment and new drug are used until disease progression In addition, in that particular case, the FAD states: ”The committee considered that the unprecedented survival benefit with the addition of pertuzumab should be considered in the light of modest life expectancy of these patients and concluded that it was fair and reasonable to accept that pertuzumab fulfils the end-of-life criteria”. It should be noted that the control arm of the company analysis presented estimates of much greater than the 24 months (unadjusted median overall survival in the control arm of CLEOPATRA was 40.8 months) [27] whereas the majority of the analysis presented by MSD are either much closer to or below 24 months. Additional evidence from TA462 in classical Hodgkin’s lymphoma also suggests the potential flexibility associated with these criteria where there is a significant unmet need [28]. The mean life years of the patients with SoC in the economic model presented was 2.3 years which is greater than the 24 months specified in the NICE end of life criteria[28].. The committee acknowledged that the product did not unequivocally meet the criterion for short life expectancy but that it was plausible that the criterion could apply. It therefore agreed that on balance, nivolumab met the criterion for short life expectancy, and took this into account in its decision-making. [28] Given the lack of new squamous NSCLC treatment options for decades and the prognosis remaining poor, it should be considered that a 1L IO option with proven efficacy fulfils an unmet need.
Does pembrolizumab combination therapy extend life for more than 3 months compared with standard care?	Data from KEYNOTE-407 demonstrate that pembrolizumab combination extends life by more than 3 months (median OS gain of 4.6 months) [21]

	The CS base case analysis showed an extension of 2.27 years to life of pembrolizumab combination versus SoC. In both the ERG's preferred optimistic and pessimistic analysis, the extension to life estimate is greater than 3 months.
Issue 8: Cancer Drugs Fund	
Is there further data being collected that could reduce uncertainty surrounding longer term effectiveness and health outcomes in this population?	Data from the final analysis of KEYNOTE-407 is expected to be available academic/commercial in confidence information removed, however this is an event driven trial and this timeline may change. It is also expected that further data cuts would be available post final analysis although the timeline of this is not yet available. This would provide further follow up on the overall survival of the patients in this population.
When will these additional data become available?	Further analysis due as per the comment above.
How suitable is the technology for use in the Cancer Drugs Fund (CDF)?	As per the point above, given the fact that additional data is planned to be collected which might reduce some of the uncertainties highlighted in the technical report, this technology is suitable for the CDF.

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ID1306 Technical Engagement Evidence Supporting Document

Table 1 and Table 2 below show the scenario analysis (S.A) as described in the technical report response document.

Table 1. Scenario Analyses for the overall population – Comparison versus Standard of Care (SoC)

		Pembrolizumab combination			SoC			Pembrolizumab combination vs SoC		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Scenario 1.a	As per CS base case with amends 1-4	£71,778	4.01	2.94	£28,488	1.76	1.27	£43,290	1.68	£25,828
Scenario 1.b	As S.A 1.a plus KN407 PB utility	£71,778	4.01	2.69	£28,488	1.76	1.20	£43,290	1.49	£29,099
Scenario 1.c	As S.A 1.a plus treatment effect duration 3 years post discontinuation	£66,550	3.29	2.42	£28,488	1.76	1.27	£38,061	1.15	£33,075
Scenario 1.d	S.A 1.b and 1.c combined	£66,550	3.29	2.26	£28,488	1.76	1.20	£38,061	1.06	£35,839
Scenario 2.a	As per CS base case with amends 1-4 plus ERG optimistic survival analysis (KM/SEER applied to SoC arm and KM/log-logistic applied to pembrolizumab combination arm)	£66,262	3.26	2.39	£28,488	1.76	1.27	£37,774	1.12	£33,663
Scenario 2.b	As S.A 2.a plus KN407 PB utility	£66,262	3.26	2.24	£28,488	1.76	1.20	£37,774	1.04	£36,316
Scenario 2.c	As S.A 2.a plus treatment effect duration 3 years post discontinuation	£65,590	3.17	2.32	£28,488	1.76	1.27	£37,102	1.05	£35,185
Scenario 2.d	S.A 2.b and 2.c combined	£65,590	3.17	2.19	£28,488	1.76	1.20	£37,102	0.99	£37,656

Table 2. Scenario analyses for the subgroup with PD-L1 expression ≥50% - Comparison versus pembrolizumab monotherapy

		Pembrolizumab monotherapy			Pembrolizumab combination			Pembrolizumab combination vs Pembrolizumab monotherapy		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. QALYs	ICER
Scenario 1.a	As per CS base case with amends 1-4	£74,972	3.75	2.74	£69,481	3.89	2.85	-£5,491	0.12	Dominant
Scenario 1.b	As S.A 1.a plus KN407 PB utility	£74,972	3.75	2.37	£69,481	3.89	2.55	-£5,491	0.18	Dominant
Scenario 1.c	As S.A 1.a plus treatment effect duration 3 years post discontinuation	£70,183	3.10	2.27	£64,311	3.19	2.34	-£5,873	0.08	Dominant
Scenario 1.d	S.A 1.b and 1.c combined	£70,183	3.10	2.00	£64,311	3.19	2.14	-£5,873	0.14	Dominant
Scenario 2.a	As per CS base case with amends 1-4 plus ERG optimistic survival analysis (KM/SEER applied to SoC arm and KM/log-logistic applied to pembrolizumab combination arm)	£70,808	3.18	2.33	£65,187	3.31	2.43	-£5,621	0.10	Dominant
Scenario 2.b	As S.A 2.a plus KN407 PB utility	£70,808	3.18	2.04	£65,187	3.31	2.21	-£5,621	0.16	Dominant
Scenario 2.c	As S.A 2.a plus treatment effect duration 3 years post discontinuation	£72,634	3.43	2.50	£66,925	3.54	2.60	-£5,709	0.09	Dominant
Scenario 2.d	S.A 2.b and 2.c combined	£72,634	3.43	2.19	£66,925	3.54	2.34	-£5,709	0.16	Dominant

Issue 2: Place in the treatment pathway of pembrolizumab combination therapy

Would it be more appropriate to use pembrolizumab combination therapy as a first line treatment option for patients who do not have strong PD-L1 expression (TPS <1% and 1-49%), or to reserve immunotherapy as a treatment option at second-line?

Median OS was longer in the pembrolizumab combination than the control, in each of the PD-L1 <1% (15.9 vs 10.2 months) and PD-L1 1-49% (14.0 vs 11.6 months) subgroups. In the PD-L1 ≥50% subgroup, the median OS was not reached in either the pembrolizumab combination or control groups. However, the ITT population showed median OS was longer in the pembrolizumab combination compared with the control (15.9% months vs 11.3 months)(Table 3).

Table 3: Analyses of OS

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‡‡
TPS<1%							
Pembrolizumab combination	95	29 (30.5)	788.4	3.7	15.9 (13.1, .)	80.7 (70.7, 87.5)	0.61 (0.38, 0.98) p=0.0188
Control	99	44 (44.4)	762.0	5.8	10.2 (8.6, 13.8)	79.4 (69.6, 86.4)	
TPS 1-49%							
Pembrolizumab combination	103	31 (30.1)	891.5	3.5	14.0 (12.8, .)	84.5 (75.6, 90.4)	0.57 (0.36, 0.90) p=0.0079
Control	104	45 (43.3)	811.6	5.5	11.6 (8.9, 17.2)	76.0 (66.3, 83.3)	
TPS≥50%							
Pembrolizumab combination	73	23 (31.5)	616.8	3.7	Not Reached (11.3, .)	81.9 (70.9, 89.1)	0.64 (0.37, 1.10) p=0.0523
Control	73	30 (41.1)	536.4	5.6	Not Reached (7.4, .)	71.3 (59.0, 80.5)	
ITT							
Pembrolizumab combination	278	85 (30.6)	2362.3	3.6	15.9 (13.2, .)	'academic/commercial in confidence information removed'	0.64 (0.49,0.85) P=0.0008
Control	281	120 (42.7)	2160.0	5.6	11.3 (9.5, 14.8)	'academic/commercial in confidence information removed'	

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

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

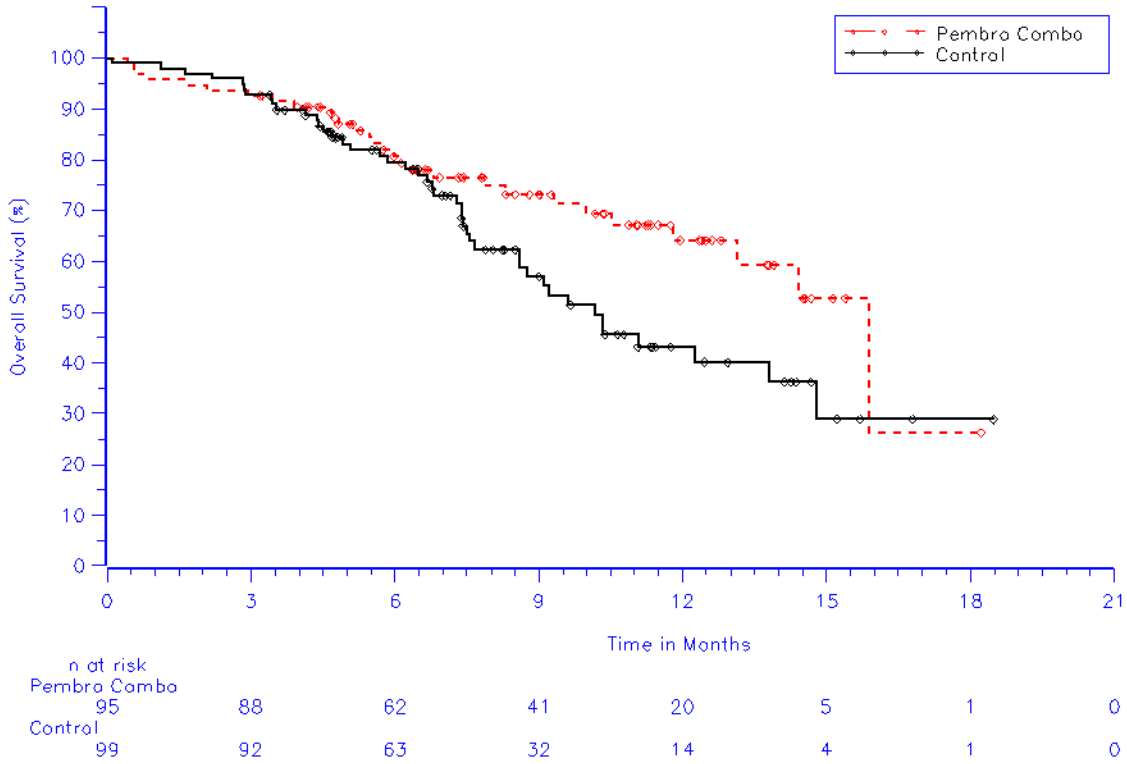
‡‡ One-sided p-value based on stratified log-rank test.

Database Cut-off Date: 03APR2018

The KM curves for all PD-L1 subgroups demonstrated a consistent effect of pembrolizumab combination over control, regardless of PD-L1 expression status. The KM curves separated

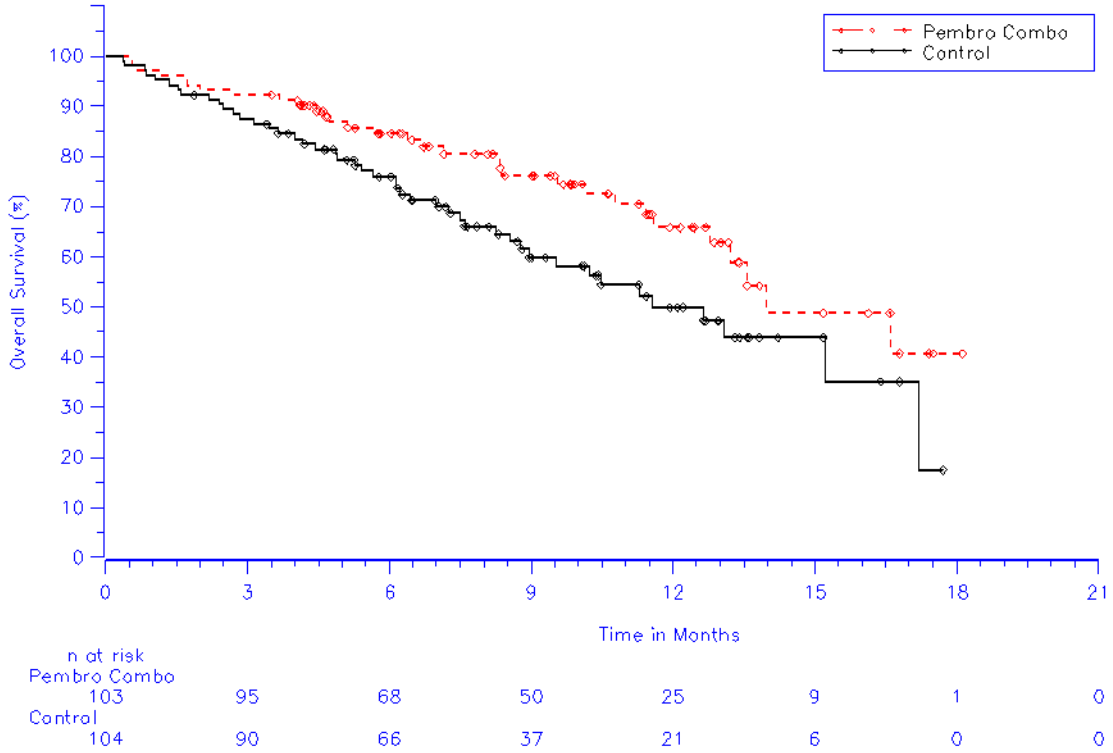
earlier as PD-L1 levels increased, after 7 months for PD-L1 <1%, after 2 months for 1-49%, and earlier than 1 month for PD-L1 ≥50% as well as the early separation seen in the ITT population remaining separated thereafter (Figure 1,Figure 2, Figure 3, Figure 4).

Figure 1. KM estimates of OS (ITT population; TPS<1%)



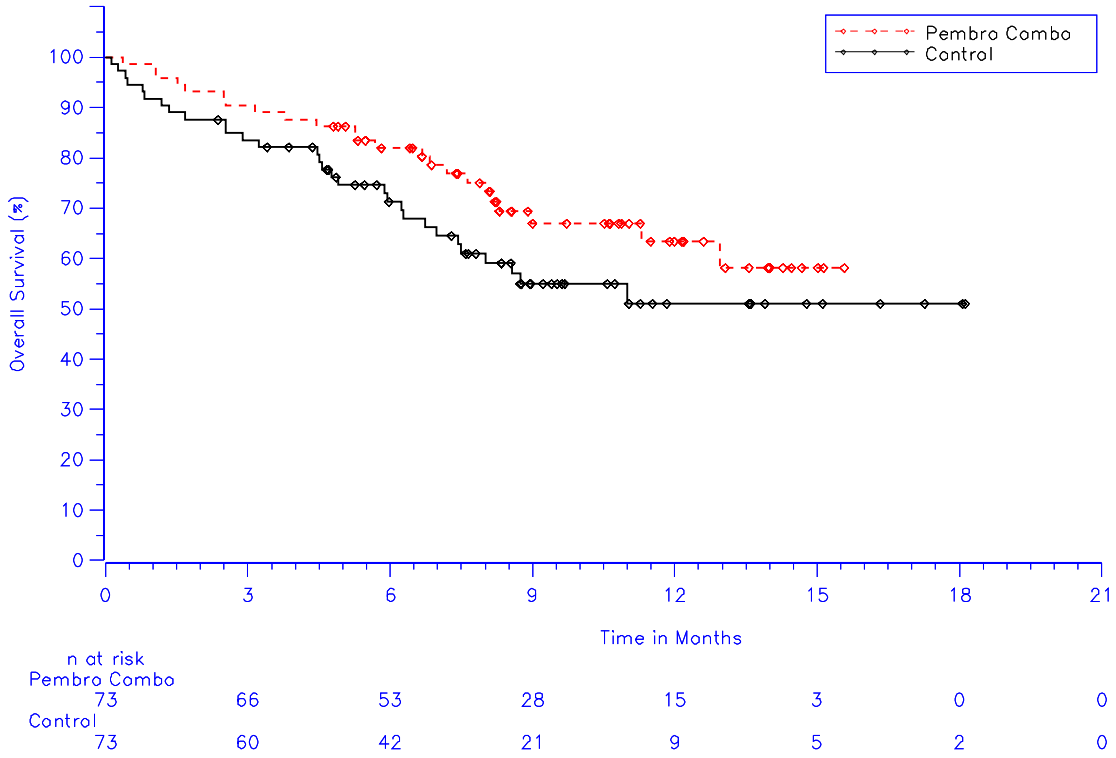
Source: Clinical study report[1]

Figure 2. KM estimates of OS (ITT population; TPS 1-49%)



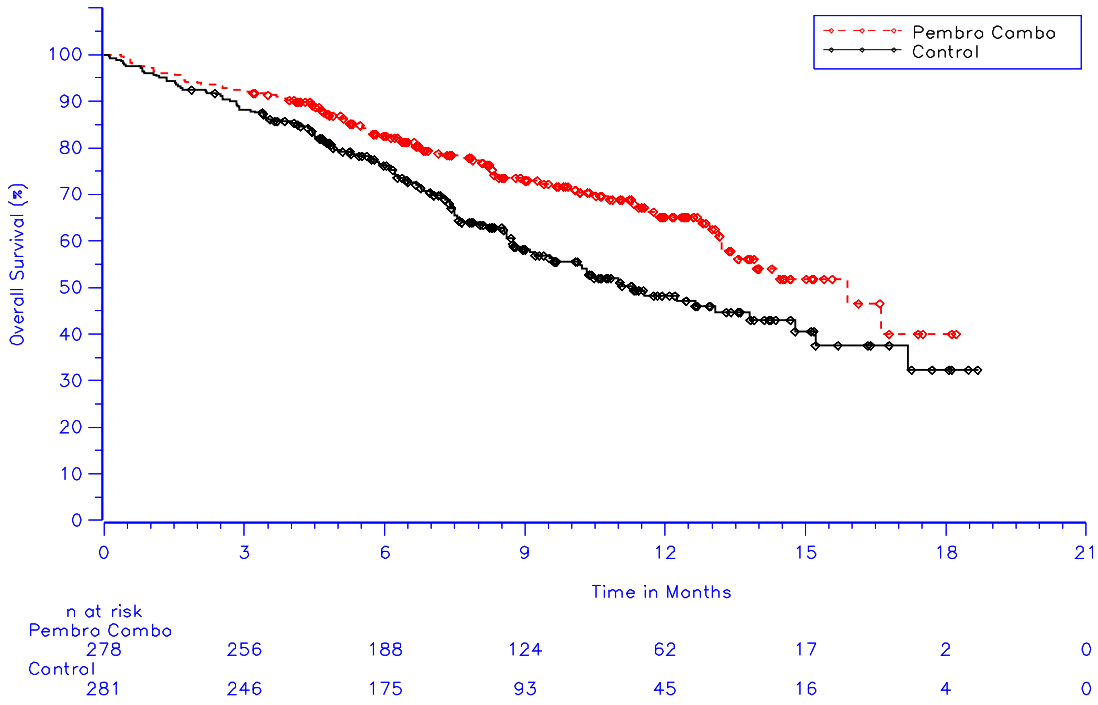
Source: Clinical study report[1]

Figure 3: KM estimates of OS (ITT population; TPS ≥50%)



Source: Clinical study report[1]

Figure 4: KM estimates of OS (ITT population)



Source: Clinical study report[1]

Based on BICR assessment, median PFS for pembrolizumab combination was 6.4 months (95% CI 6.2, 8.3) compared with 4.8 months (95% CI 43, 5.7) for the control arm. This was a statistically significant and clinically meaningful benefit in PFS, equating to a 44% reduction in risk of progression or death for the pembrolizumab combination compared with the control (HR 0.56; 95% CI: 0.45, 0.70; p<0.0001) (Table 4).

The KM plots for PFS based on BICR assessment demonstrated that the pembrolizumab combination curve separated from the control curve in PD-L1 ≥50% at week 0 and at week 6 for the ITT population which were sustained throughout the remainder of the evaluation period (Figure 5, Figure 6, Figure 8, Figure 8).

Table 4: Analysis of PFS based on BICR per RECIST 1.1 (ITT population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Month 6 in %† (95% CI)	vs. Control Hazard Ratio‡ (95% CI)‡ p-value‡‡
TPS<1%							
Pembrolizumab combination	95	55 (57.9)	557.1	9.9	6.3 (6.1, 6.5)	65.7 (54.6, 74.7)	0.68 (0.47, 0.98) p=0.0177
Control	99	67 (67.7)	508.9	13.2	5.3 (4.4, 6.2)	46.7 (35.8, 57.0)	

TPS 1-49%							
Pembrolizumab combination	103	54 (52.4)	656.7	8.2	7.2 (6.0, 11.4)	61.9 (51.1, 71.0)	0.56 (0.39, 0.80) p=0.0008
Control	104	73 (70.2)	526.5	13.9	5.2 (4.2, 6.2)	48.8 (38.3, 58.4)	
TPS >50%							
Pembrolizumab combination	73	39 (53.4)	449.4	8.7	8.0 (6.1, 10.3)	67.0 (54.2, 77.0)	0.37 (0.24, 0.58) p<0.0001
Control	73	55 (75.3)	296.8	18.5	4.2 (2.8, 4.6)	23.0 (13.3, 34.2)	
ITT							
Pembrolizumab combination	278	152 (54.7)	1716.9	8.9	6.4 (6.2, 8.3)	'academic/commercial in confidence information removed'	0.56 (0.45, 0.70) p<0.0001
Control	281	197 (70.1)	1358.1	14.5	4.8 (4.3, 5.7)	'academic/commercial in confidence information removed'	

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

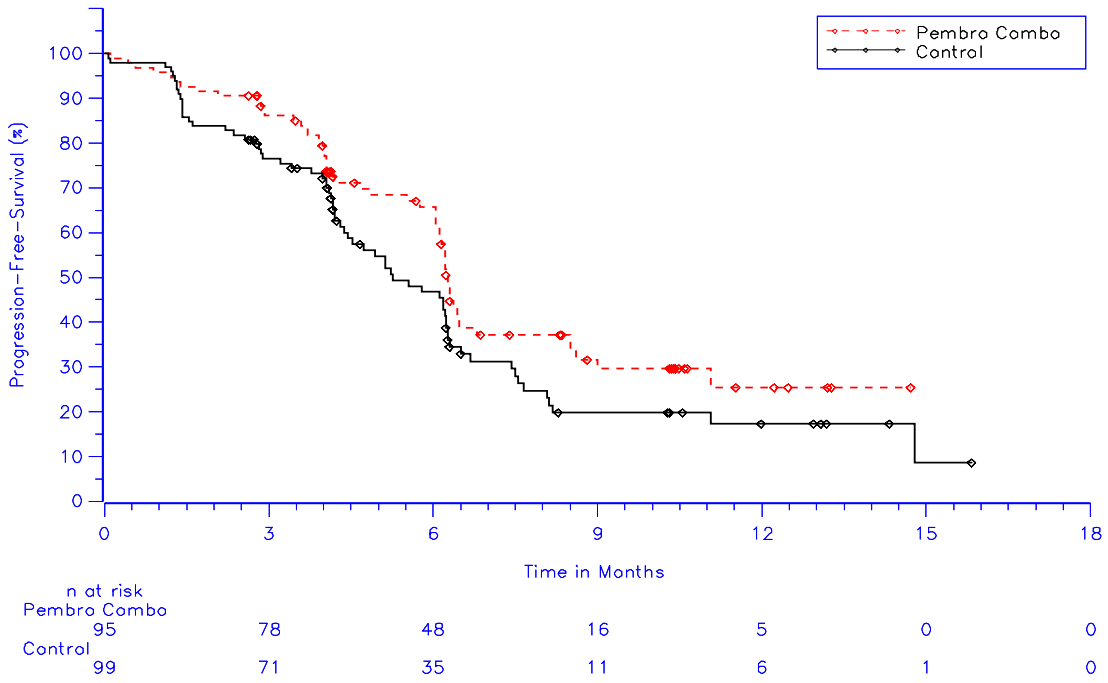
‡ Based on Cox regression model with treatment as covariate stratified by PD-L1 status (TPS ≥ 1% vs. < 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and geographic region (East Asia vs. non-East Asia).

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

Database Cut-off Date: 03APR2018

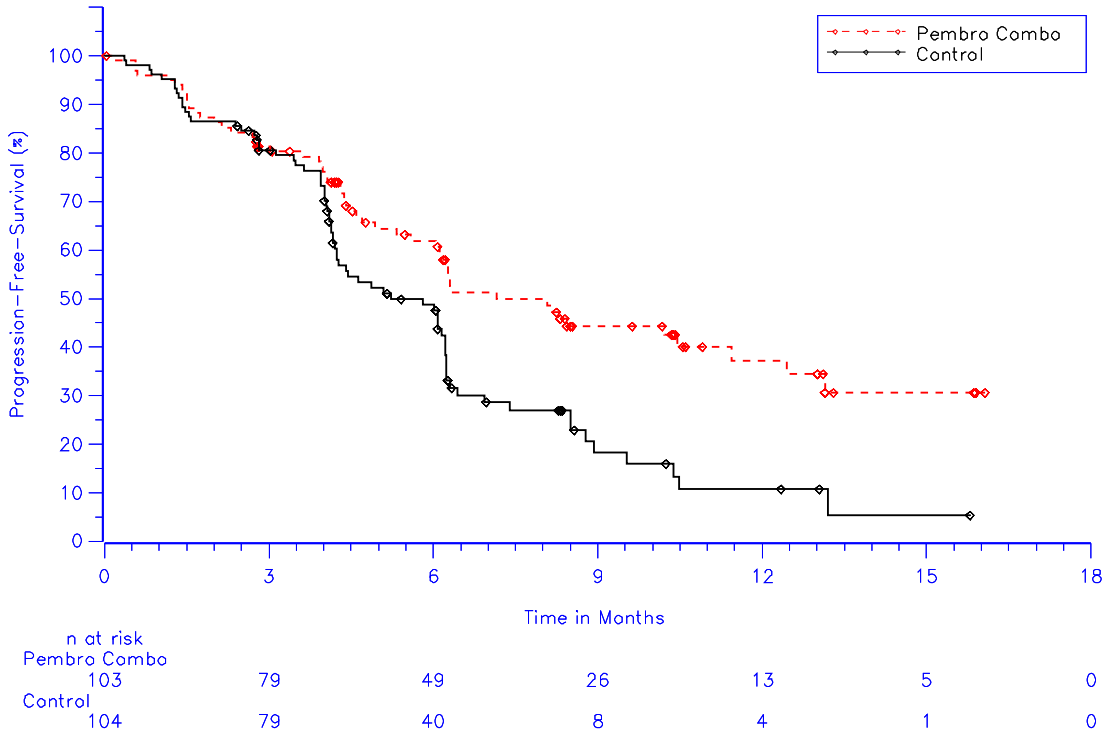
Source: Clinical study report[1]

Figure 5: Kaplan-Meier estimates of PFS based on BICR per RECIST 1.1 (ITT population; TPS<1%)



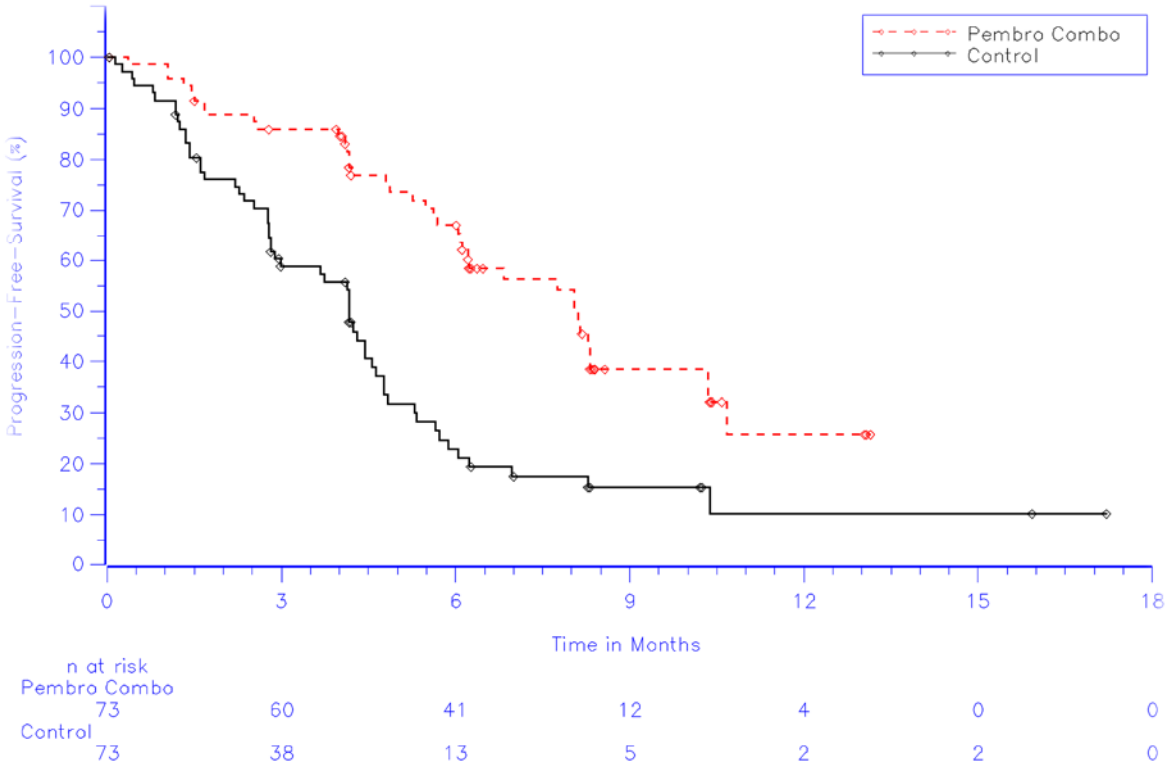
Source: Clinical study report[1]

Figure 6: Kaplan-Meier estimates of PFS based on BICR per RECIST 1.1 (ITT population; TPS 1-49%)



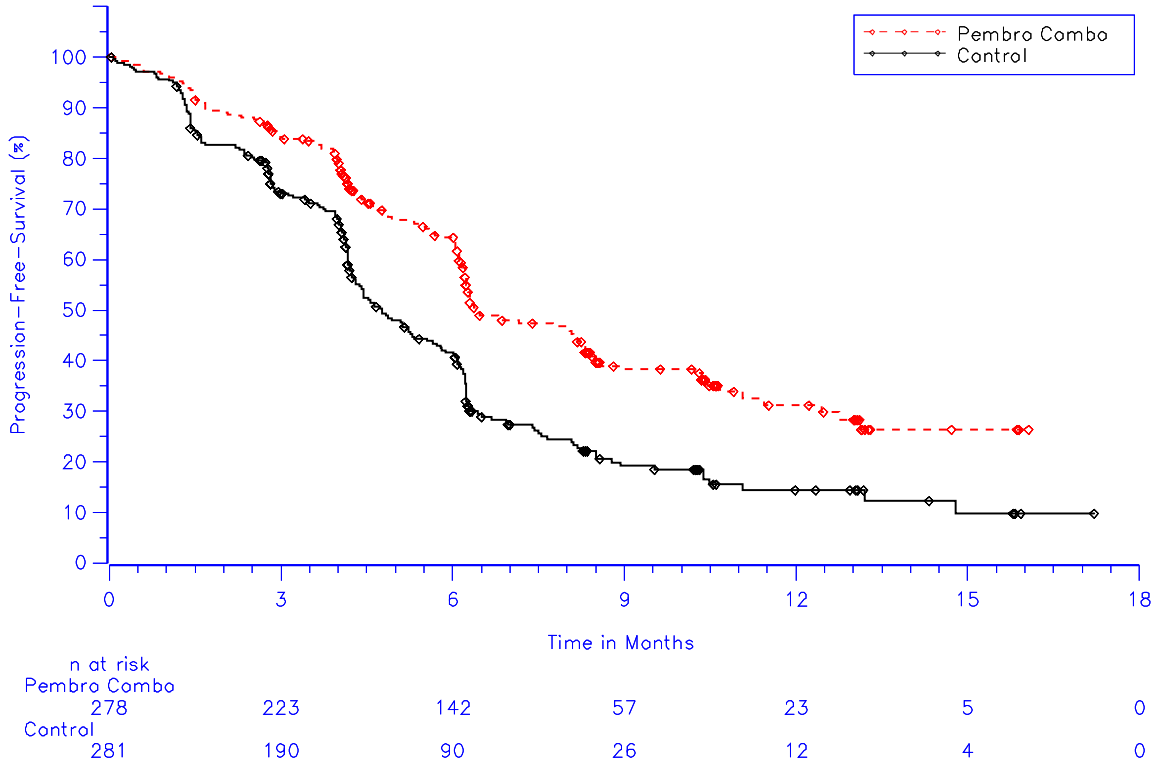
Source: Clinical study report[1]

Figure 7: Kaplan-Meir of PFS based on BICR per RECIST 1.1 (ITT population; TPS >50%)



Source: Clinical study report[1]

Figure 8: Kaplan-Meier estimates of PFS based on BICR per RECIST 1.1 (ITT population)



Source: Clinical study report[1]

Evidence submitted in **Error! Reference source not found.** below shows it is more appropriate to use IO as a 1L treatment option rather than reserve it as a 2L treatment option. There were a larger number of patients who discontinued treatment due to progressive disease, adverse event and physician decision who received no further 2L treatment in the control arm compared to the pembrolizumab combination arm. These results imply that these patients were not well enough to receive further 2L therapy, therefore if IO was to be reserved as a 2L option, the pool of patients who would could benefit from IO would be smaller.

Table 5: Utilization of New Oncologic Therapies after Discontinuing from Study Treatment (ASaT Population) [2]

'academic/commercial in confidence information removed'

Issue 3 Subsequent treatments

What percentage of people, who receive first-line standard chemotherapy treatment, would be expected to receive second-line immunotherapy following disease progression?

Table 5 also highlights, as per the proportions of patients receiving subsequent therapy in the model, that out of those who discontinued therapy ('academic/commercial in confidence information removed' in the pembrolizumab combination arm and 208 in the control arm), approximately 'academic/commercial in confidence information removed' of patients in the

pembrolizumab combination arm were receiving 2L chemotherapy and 'academic/commercial in confidence information removed' in the control arm were receiving any 2L therapy which could have included: 2L IO, chemotherapy or both. These proportions of patients who were receiving 2L treatment, discontinued due to progressive disease, adverse event or physician decision. These proportions are in line with clinical expert testimony.

Table 6 highlights that of the remaining 208 participants who discontinued study treatment in the control group, 75 eligible participants who had disease progression verified by BICR crossed over to pembrolizumab monotherapy within the study.

An additional 14 participants received a checkpoint inhibitor (pembrolizumab, atezolizumab, or nivolumab) as subsequent therapy outside of the study. A total of 'academic/commercial in confidence information removed' participants in the control group are shown as receiving a subsequent checkpoint inhibitor. However 'academic/commercial in confidence information removed' crossed over to pembrolizumab monotherapy within the study before receiving Atezolizumab outside of the study; therefore a total of 'academic/commercial in confidence information removed'participants were included in the crossover calculations. Thus, 42.8% ('academic/commercial in confidence information removed') of participants in the control who discontinued study treatment crossed over to a checkpoint inhibitor. Broadly in line with the estimates provided by clinicians.

Table 6: Disposition of subjects (ITT)

	Pembro Combo n (%)	**Control n (%)**
Subjects in population	278	281
Status for Study Medication of Treatment Phase		
Started	278	280
Discontinued	157 (56.5)	208 (74.3)
Adverse Event	48 (17.3)	25 (8.9)
Clinical Progression	13 (4.7)	26 (9.3)
Lost To Follow-Up	0 (0.0)	2 (0.7)
Physician Decision	5 (1.8)	6 (2.1)
Progressive Disease	86 (30.9)	140 (50.0)
Withdrawal By Subject	5 (1.8)	9 (3.2)
Ongoing†	121 (43.5)	72 (25.7)
Status for Study Medication of Crossover Phase		
Subjects who Crossed Over Discontinued Adverse Event Clinical Progression Progressive Disease Withdrawal By Subject Ongoing‡	'academic/commercial in confidence information removed'	
Status for Trial		
Discontinued Adverse Event Death	'academic/commercial in confidence information removed'	

	Pembro Combo n (%)	Control n (%)
Lost To Follow-Up Physician Decision Withdrawal By Subject Ongoing[§]		

[†] Status was not reported as of the cutoff date. Subjects could be ongoing with study treatment.
[‡] Status was not reported as of the cutoff date. Subjects could be ongoing with pembrolizumab monotherapy.
[§] Status was not reported as of the cutoff date. Subjects could be ongoing with study.
For the status for study medication of treatment phase, subjects treated with study medication is used as the denominator for percentage calculation.
For the status for study medication of crossover phase, subjects who crossed over is used as the denominator for percentage calculation.
For the status for trial, subjects in population is used as the denominator for percentage calculation.
Database Cutoff Date: 03APR2018

Source: Clinical study report

Source: Clinical study report[1]

How long would these people be expected to be treated with second-line immunotherapy?

In the KEYNOTE-407 trial participants who crossed over from the control arm to pembrolizumab monotherapy had a mean duration of treatment of 'academic/commercial in confidence information removed' days Table 7.

Table 7: Duration of Pembrolizumab Monotherapy - Within Trial (Crossover Population)[2]

'academic/commercial in confidence information removed'

*Which second-line immunotherapies would be used and in what proportions***?**

Table 8: Summary of subsequent antineoplastic therapy (ITT population)

	Pembro Combo n (%)	Control n (%)
Subjects in population	278	281
With one or more subsequent medications With no subsequent medication	'academic/commercial in confidence information removed'	
antineoplastic and immunomodulating agents		
antineoplastic agents atezolizumab carboplatin cisplatin docetaxel	'academic/commercial in confidence information removed'	

	Pembro Combo		Control	
	n	(%)	n	(%)
gefitinib gemcitabine gimeracil (+) oteracil potassium (+) tegafur hydrazine sulfate nivolumab paclitaxel pembrolizumab pemetrexed disodium ramucirumab vinorelbine tartrate				
Every subject is counted a single time for each applicable specific concomitant medication. A subject with multiple concomitant medications within a medication category is counted a single time for that category. A medication class or specific medication appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. Database Cutoff Date: 03APR2018				

Source: Clinical study report[1]

Issue 5: Network Meta-analysis (NMA) for comparators

Should the trials including an ECOG performance status of 2 be excluded or adjusted for to minimise the risk of bias?

It was necessary to include trials that enrolled patients with an ECOG PS of 2 in order to form connected networks of evidence with the relevant comparators. For example, in the pure squamous network for OS, all connections between pembro + carboplatin + pac/nab-pac and other interventions (carb + gem, cis + gem, cis + doc, cis + pac, and carb + pac/nab-pac) are informed by either Saad 2017 (26.8% ECOG PS 2) or ECOG 1594 (5.5% ECOG PS 2). Consequently, the decision was made to exclude only trials in which greater than 50% of patients had an ECOG performance status of 2. This decision was consistent with the KEYNOTE-024 and KEYNOTE-189 submissions to NICE which were accepted by the committee.

While this data is limited, there does not seem to be a correlation between the proportion of patients with an ECOG PS of 2 and the treatment effect. This suggests that the imbalance in the distribution of ECOG scores between trials does not bias the NMA.

Table 9: HRs for cis+gem vs. carb+gem and corresponding percentage of patients with ECOG PS 2

Trial	HR for cis + gem vs. carb + gem	Percentage of patients with ECOG PS 2
Ferry 2017[3]	0.93	7.5%
Mazzanti 2003[4]	0.87	17.5%
Zatloukal 2003[5]	1.01	NR
Saad 2017[6]	0.98	26.8%

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6. Saad AS, Ghali RR, Shawki MA. A prospective randomized controlled study of cisplatin versus carboplatin-based regimen in advanced squamous nonsmall cell lung cancer. Journal of cancer research and therapeutics. 2017;13(2):198-203.

Dear Alistair,

I hope this finds you well. I am the technical lead for NICE's technology appraisal of **Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer.**

I understand that you are a nominated clinical expert for this topic.

This is one of the first appraisals to go through our new process, which involves a 'technical engagement' stage. We are seeking your clinical expert opinion to help us write a technical report which will cover all the key issues we think are important for this topic. I was wondering whether you would be happy to provide your input on the below questions? You can return your responses via email or alternatively I could call you to talk through the questions over the phone. Please let me know your preference.

We would be very grateful if you could return your answers to us by **5pm Wednesday 6 February.** Please don't hesitate to contact me if you have any questions, or if you would like to schedule a call to discuss the questions.

Once again, thank you for your input on this appraisal – your time and expertise are very much appreciated.

Best wishes,

Alan Moore

1. **Standard chemotherapy comparability**:

   Within the pivotal clinical trial (KEYNOTE 407), the comparator is carboplatin with either paclitaxel or nab-paclitaxel. NICE are aware that there is a range of standard chemotherapies available for use within the NHS (docetaxel, gemcitabine, paclitaxel or vinorelbine)
   Clinical advice sought by the company suggests that carboplatin plus paclitaxel/nab-paclitaxel can be considered equal in outcomes to the range of chemotherapies mentioned above.

   - Do you consider that carboplatin plus paclitaxel/nab-paclitaxel can be considered equal in terms of outcomes to the range of chemotherapy treatment regimens currently used in the NHS for untreated metastatic squamous non-small-cell lung cancer? If not please explain.
   - Do you consider carboplatin to be equal in terms of outcomes to cisplatin? If not please explain.
   - Do you consider paclitaxel and nab-paclitaxel to be equal to each other in terms of outcomes? If not please explain.

- What influences the choice of chemotherapy treatment regimens given to people in the NHS with untreated metastatic squamous non-small-cell lung cancer?
- Could you provide an estimate of the proportions in which different standard chemotherapies are used in the NHS for untreated metastatic squamous non-small-cell lung cancer?

2. **Optimal timing of treatment**:

   Clinical advisors to the ERG stated that there was uncertainty regarding the optimal timing for the use of pembrolizumab combination therapy, should it be recommended as a treatment option in this population. Evidence from the KEYNOTE 407 trial show that for those patients in the PD-L1 TPS <1% and 1-49% subgroups, the separation occurs later than in the ≥50% subgroup (at month 0 for TPS ≥50%, after 2 months for 1-49%, and after 7 months for TPS <1%). This indicates a delayed treatment effect in lower PD-L1 TPS subgroups.

   Clinical advisors to the Evidence Review Group (ERG) highlighted that, at present, people in England may receive treatment with only one immunotherapy drug. If pembrolizumab combination therapy were to be recommended by NICE (irrespective of PD-L1 status), there may be uncertainty about whether it is optimal to offer first-line pembrolizumab combination therapy to patients who do not have strong PD-L1 expression (TPS <1% and 1-49%), or to reserve immunotherapy as a treatment option at second-line, given the additional toxicity burden of pembrolizumab in addition to standard care chemotherapy.

   For people with PD-L1 TPS ≥50%, clinical advisors to the ERG noted that pembrolizumab monotherapy may be preferred as first line treatment, as it may be considered to be as clinically effective as pembrolizumab combination therapy and is associated with less toxicity.

   - Would it be more appropriate to use pembrolizumab combination therapy as a first line treatment option for patients who do not have strong PD-L1 expression (TPS <1% and 1-49% subgroups), or to reserve immunotherapy as a treatment option at second-line?
   - Would it be more appropriate to use pembrolizumab as first-line combination therapy or as monotherapy for patients with PD-L1 strong expression (TPS **≥**50%)?

3. **Most plausible treatment effect duration after stopping of pembrolizumab combination therapy**:

   The company's economic model has assumed a lifetime treatment benefit for pembrolizumab combination therapy after treatment has been stopped.

Clinical advisors to the ERG have stated that this is likely to be over optimistic. The NICE technical team are aware that in previous lung cancer appraisals (e.g. pembrolizumab for PD-L1-positive NSCLC after chemotherapy [TA428] considered 3 years realistic while atezolizumab for NSCLC after chemotherapy [TA520] considered 5 years), the committee have preferred to assume a 3-5 year treatment effect duration, commencing after treatment discontinuation.

- What would you consider to be the most plausible treatment effect duration?

4. **Overall survival**

A key determinant of cost-effectiveness for pembrolizumab combination therapy is overall survival outcomes. As the trial evidence submitted to us by the company is of short duration, there is considerable uncertainty around long term survival estimates.

The ERG received opinions from three clinical advisors regarding their estimates of overall survival and progression-free survival. These estimates can be seen in the table below;

	Clinical Advisor 1		**Clinical Advisor 2**		**Clinical Advisor 3**	
Overall Survival	**5 years**	**10 years**	**5 years**	**10 years**	**5 years**	**10 years**
Pembrolizumab combination	20%	11%	20%	11%	15-20%	5-10%
Standard care	8%	3%	8%	3%	8-10%	5%
Progression-free survival	**5 years**	**10 years**	**5 years**	**10 years**	**5 years**	**10 years**
Pembrolizumab combination	10%	-	10%	-	10%	-
Standard care	3%	-	3%	-	3%	-

- What do you believe are the most plausible estimates for overall survival and progression-free survival at 5 years and 10 years? Could you also provide an estimate for these outcomes at 20 years?
- How difficult is it for you to give these estimates? How uncertain are they?

The ERG notes that in the company's projected survival analysis, 6% of patients are assumed to be cured after 18 years (in that their risk of death is equal to members of the general public of the same age). Is this estimate plausible? Do you have a different estimate? Is treatment with pembrolizumab combination likely to be curative in a small proportion of people?

Dear Alistair,

I hope this finds you well. I am the technical lead for NICE's technology appraisal of **Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer.**

I understand that you are a nominated clinical expert for this topic.

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1. **Standard chemotherapy comparability**:

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   Clinical advice sought by the company suggests that carboplatin plus paclitaxel/nab-paclitaxel can be considered equal in outcomes to the range of chemotherapies mentioned above.

   - Do you consider that carboplatin plus paclitaxel/nab-paclitaxel can be considered equal in terms of outcomes to the range of chemotherapy treatment regimens currently used in the NHS for untreated metastatic squamous non-small-cell lung cancer? If not please explain.

   Yes. The meta-analysis from Treat et al Lung Cancer, 2012; 76 (2), 222–227 suggests they all platinum combinations except with pemetrexed are roughly equaivalent

   - Do you consider carboplatin to be equal in terms of outcomes to cisplatin? If not please explain.

Yes. See above.

- Do you consider paclitaxel and nab-paclitaxel to be equal to each other in terms of outcomes? If not please explain.

  There are some differences in toxicity profile but I am not convinced there is any major difference in efficacy in squamous cancers. Nab-paclitaxel may be deliverable to an older patient population

- What influences the choice of chemotherapy treatment regimens given to people in the NHS with untreated metastatic squamous non-small-cell lung cancer?

  Much of it is tradition; the UK has tended to use carboplatin and gemcitabine whilst USA has been stronger user of carboplatin and paclitaxel. The gemcitabine regimen is often preferred due to lack of alopecia and neuropathy in the UK

- Could you provide an estimate of the proportions in which different standard chemotherapies are used in the NHS for untreated metastatic squamous non-small-cell lung cancer?

  For 1st line I suspect it will be 80% Carboplatin- gemcitabine, 10% carboplatin-vinorelbine and 10% others including Carboplatin-paclitaxel

2. **Optimal timing of treatment**:

   Clinical advisors to the ERG stated that there was uncertainty regarding the optimal timing for the use of pembrolizumab combination therapy, should it be recommended as a treatment option in this population. Evidence from the KEYNOTE 407 trial show that for those patients in the PD-L1 TPS <1% and 1-49% subgroups, the separation occurs later than in the ≥50% subgroup (at month 0 for TPS ≥50%, after 2 months for 1-49%, and after 7 months for TPS <1%). This indicates a delayed treatment effect in lower PD-L1 TPS subgroups.

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   For people with PD-L1 TPS ≥50%, clinical advisors to the ERG noted that pembrolizumab monotherapy may be preferred as first line treatment, as it may be considered to be as clinically effective as pembrolizumab combination therapy and is associated with less toxicity.

- Would it be more appropriate to use pembrolizumab combination therapy as a first line treatment option for patients who do not have strong PD-L1 expression (TPS <1% and 1-49% subgroups), or to reserve immunotherapy as a treatment option at second-line?

  In fit patients it would be more appropriate to use chemotherapy-pembrolizumab combination in the 1st line setting as separation occurring despit cross-over and a number of patients may not be fit for 2nd line immunotherapy if used in the 2nd line setting.

- Would it be more appropriate to use pembrolizumab as first-line combination therapy or as monotherapy for patients with PD-L1 strong expression (TPS ≥50%)?

  This is a more difficult question and is the subject of some debate. It may depend on other factors such as disease burden, site of disease etc. I suspect a one-size fits all policy may not be the most appropriate

3. **Most plausible treatment effect duration after stopping of pembrolizumab combination therapy**:

   The company's economic model has assumed a lifetime treatment benefit for pembrolizumab combination therapy after treatment has been stopped. Clinical advisors to the ERG have stated that this is likely to be over optimistic. The NICE technical team are aware that in previous lung cancer appraisals (e.g. pembrolizumab for PD-L1-positive NSCLC after chemotherapy [TA428] considered 3 years realistic while atezolizumab for NSCLC after chemotherapy [TA520] considered 5 years), the committee have preferred to assume a 3-5 year treatment effect duration, commencing after treatment discontinuation.

- What would you consider to be the most plausible treatment effect duration?

  I agree a 3-5 year duration of treatment effect seems most plausible.

4. **Overall survival**

   A key determinant of cost-effectiveness for pembrolizumab combination therapy is overall survival outcomes. As the trial evidence submitted to us by the company is of short duration, there is considerable uncertainty around long term survival estimates.

   The ERG received opinions from three clinical advisors regarding their estimates of overall survival and progression-free survival. These estimates can be seen in the table below;

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Pembrolizumab combination	10%	-	10%	-	10%	-
Standard care	3%	-	3%	-	3%	-

- What do you believe are the most plausible estimates for overall survival and progression-free survival at 5 years and 10 years?

I think those figures are probably relatively reasonable.

	AG		
Overall Survival	**5 years**	**10 years**	**20 years**
Pembrolizumab combination	20%	11%	4%
Standard care	8%	3%	0%
Progression-free survival	**5 years**	**10 years**	
Pembrolizumab combination	10%	5%	4%
Standard care	3%	0%	0%

Could you also provide an estimate for these outcomes at 20 years?

- How difficult is it for you to give these estimates?

Very difficult. We are still obtaining long term survival data from the initial patients treated with single agent IO. All data with Chemo-IO

combinations is relatively immature and represents patients treated in the the trial setting. We are still learning if these can be translated to the real world setting (early evidence would suggest they can be)

- How uncertain are they?

  Very uncertain; see comments above

  The ERG notes that in the company's projected survival analysis, 6% of patients are assumed to be cured after 18 years (in that their risk of death is equal to members of the general public of the same age). Is this estimate plausible? I

  I think so. Emerging data is that a small number of patients may be cured from treatment with pembrolizumab and likely to be the same with chemotherapy-IO combinations. Numbers are difficult to determine as is proportion that are alive in this patient group as often have other co-morbidities such as heart disease and secondary maliganncies

  Do you have a different estimate? Is treatment with pembrolizumab combination likely to be curative in a small proportion of people?

Dear [redacted],

I hope this finds you well. I am the technical lead for NICE's technology appraisal of **Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer.**

I understand that you are a nominated clinical expert for this topic.

This is one of the first appraisals to go through our new process, which involves a 'technical engagement' stage. We are seeking your clinical expert opinion to help us write a technical report which will cover all the key issues we think are important for this topic. I was wondering whether you would be happy to provide your input on the below questions? You can return your responses via email or alternatively I could call you to talk through the questions over the phone. Please let me know your preference.

We would be very grateful if you could return your answers to us by **5pm Friday 1st February.** Please don't hesitate to contact me if you have any questions, or if you would like to schedule a call to discuss the questions.

Once again, thank you for your input on this appraisal – your time and expertise are very much appreciated.

Best wishes,

Alan Moore

1. **Standard chemotherapy comparability**:

   Within the pivotal clinical trial (KEYNOTE 407), the comparator is carboplatin with either paclitaxel or nab-paclitaxel. NICE are aware that there is a range of standard chemotherapies available for use within the NHS (docetaxel, gemcitabine, paclitaxel or vinorelbine)
   Clinical advice sought by the company suggests that carboplatin plus paclitaxel/nab-paclitaxel can be considered equal in outcomes to the range of chemotherapies mentioned above.

   - Do you consider that carboplatin plus paclitaxel/nab-paclitaxel can be considered equal in terms of outcomes to the range of chemotherapy treatment regimens currently used in the NHS for untreated metastatic squamous non-small-cell lung cancer? If not please explain.

     A. In all studies of advanced squamous NSCLC: platinum doublets have been equivalent in efficacy including carboplatin/paclitaxel. Toxicities and schedule of administration do differ. In particular there is alopecia (hair loss) with carboplatin/paclitaxel which you do not see with other platinum doublets.

- Do you consider carboplatin to be equal in terms of outcomes to cisplatin? If not please explain.

  A. In advanced disease, there is no clinically meaningful difference between cisplatin/carboplatin. Level 1 evidence meta-analysis data: *JNCI: Journal of the National Cancer Institute*, Volume 99, Issue 11, 6 June 2007, Pages 847–857, https://doi.org/10.1093/jnci/djk196.

  There my be better response rates in squamous lung cancer when cisplatin is used in particularly with radiotherapy, cisplatin is important as a radiosensitizer when giving radical radiotherapy.

- Do you consider paclitaxel and nab-paclitaxel to be equal to each other in terms of outcomes? If not please explain.

  A. Nab-paclitaxel (albumin-bound paclitaxel) has less nephropathy than solvent based paclitaxel. It has shown better response rates but no clinically meaningful survival advantage. It does not require steroid premedication and has shown better survival and better toxicity in the elderly. Eur J Cancer. 2016 Mar; 56: 162–171. It is best tolerated given on a weekly schedule. The greater price though would not justify marginal improvements in efficacy

- What influences the choice of chemotherapy treatment regimens given to people in the NHS with untreated metastatic squamous non-small-cell lung cancer?

  A. In general this is either platinum doublet (gemcitabine/vinorelbine/paclitaxel) or entry into clinical trial. Performance status is key with any chemotherapy assessment. Comorbidities can be higher in this subgroup as majority are smokers

- Could you provide an estimate of the proportions in which different standard chemotherapies are used in the NHS for untreated metastatic squamous non-small-cell lung cancer? I would think gem/carbo (80%) is the most commonly used but I have not interrogated SACT data for this.

2. **Optimal timing of treatment**:

   Clinical advisors to the ERG stated that there was uncertainty regarding the optimal timing for the use of pembrolizumab combination therapy, should it be recommended as a treatment option in this population. Evidence from the KEYNOTE 407 trial show that for those patients in the PD-L1 TPS <1% and 1-49% subgroups, the separation occurs later than in the ≥50% subgroup (at month 0 for TPS ≥50%, after 2 months for 1-49%, and after 7 months for TPS

<1%). This indicates a delayed treatment effect in lower PD-L1 TPS subgroups.

Clinical advisors to the Evidence Review Group (ERG) highlighted that, at present, people in England may receive treatment with only one immunotherapy drug. If pembrolizumab combination therapy were to be recommended by NICE (irrespective of PD-L1 status), there may be uncertainty about whether it is optimal to offer first-line pembrolizumab combination therapy to patients who do not have strong PD-L1 expression (TPS <1% and 1-49%), or to reserve immunotherapy as a treatment option at second-line, given the additional toxicity burden of pembrolizumab in addition to standard care chemotherapy.

For people with PD-L1 TPS ≥50%, clinical advisors to the ERG noted that pembrolizumab monotherapy may be preferred as first line treatment, as it may be considered to be as clinically effective as pembrolizumab combination therapy and is associated with less toxicity.

- Would it be more appropriate to use pembrolizumab combination therapy as a first line treatment option for patients who do not have strong PD-L1 expression (TPS <1% and 1-49% subgroups), or to reserve immunotherapy as a treatment option at second-line?

    A. If patient's PS 0-1 and no comorbidities then chemo/IO combination would be treatment of choice as only 40-50% of these patient would be fit enough to receive second line treatment. Chemo/IO appears to give higher PFS without significant increase in toxicity.

- Would it be more appropriate to use pembrolizumab as first-line combination therapy or as monotherapy for patients with PD-L1 strong expression (TPS **≥**50%)?

    A. The only patient I may consider chemo/IO with TPS>50% are those with bulky disease and as immunotherapy can take some time to gain a response, this is quicker with combination treatment.

3. **Most plausible treatment effect duration after stopping of pembrolizumab combination therapy**:

    The company's economic model has assumed a lifetime treatment benefit for pembrolizumab combination therapy after treatment has been stopped. Clinical advisors to the ERG have stated that this is likely to be over optimistic. The NICE technical team are aware that in previous lung cancer appraisals (e.g. pembrolizumab for PD-L1-positive NSCLC after chemotherapy [TA428] considered 3 years realistic while atezolizumab for NSCLC after chemotherapy [TA520] considered 5 years), the committee have preferred to assume a 3-5 year treatment effect duration, commencing after treatment discontinuation.

- What would you consider to be the most plausible treatment effect duration?

  A. The longest FU and overall survival data for immunotherapy is from the second line studies. For Keynote 010 long term survival estimates (>5 years) was 25% :

  Journal of Clinical Oncology 2017 35:7_suppl, 77-77

  For atezolizumab the actual 2 year survival was >30% and for 3 years was 20%, derived from the Poplar 2 study.

  The lifetime treatment benefit is likely <10% for 3 survival after treatment discontinuation for any cause. This maybe different for those individuals who reached 2 years of treatment and discontinued without progression.

4. **Overall survival**

   A key determinant of cost-effectiveness for pembrolizumab combination therapy is overall survival outcomes. As the trial evidence submitted to us by the company is of short duration, there is considerable uncertainty around long term survival estimates.

   The ERG received opinions from three clinical advisors regarding their estimates of overall survival and progression-free survival. These estimates can be seen in the table below;

	Clinical Advisor 1		**Clinical Advisor 2**		**Clinical Advisor 3**	
Overall Survival	**5 years**	**10 years**	**5 years**	**10 years**	**5 years**	**10 years**
Pembrolizumab combination	20%	11%	20%	11%	15-20%	5-10%
Standard care	8%	3%	8%	3%	8-10%	5%
Progression-free survival	**5 years**	**10 years**	**5 years**	**10 years**	**5 years**	**10 years**
Pembrolizumab combination	10%	-	10%	-	10%	-
Standard care	3%	-	3%	-	3%	-

- What do you believe are the most plausible estimates for overall survival and progression-free survival at 5 years and 10 years? Could you also provide an estimate for these outcomes at 20 years?

- How difficult is it for you to give these estimates? How uncertain are they?

  The ERG notes that in the company's projected survival analysis, 6% of patients are assumed to be cured after 18 years (in that their risk of death is equal to members of the general public of the same age). Is this estimate plausible? Do you have a different estimate? Is treatment with pembrolizumab combination likely to be curative in a small proportion of people?

  A: This is all speculation as we just do not have such long term data. All of us treating lung cancer have patients who have survived with advanced disease over 5 years (excluding oncogenically driven subtypes). However these are far and few. OS at 5 years likely to be 5-10% and 10 years 0%

Confirmation of clinical expert estimates

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]

Dear Alistair,

Thank you for your expert clinical input to date and for dialing into the technical engagement TC for NICE appraisal of **Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]**

During the technical engagement TC, you were asked again about what percentage of patients would you expect to be alive at 5, 10 and 20 years in the intervention and standard of care arms.

Just looking through the NICE technical team notes from that TC, it seems as though you thought that your initial estimates could be optimistic for the intervention arm of KEYNOTE-407 and that a smaller survival benefit could be expected from pembrolizumab combination therapy, and that the standard of care arm could expect a higher survival benefit that previously reported (Please see tables in this email). Please correct us if needed.

The reason this is so important is because there is high uncertainty in this appraisal and key modelling choices rest on expert clinical input. You were shown the estimates from the 3 ERG clinical advisors. ERG clinical advisors 1&2 agreed on more optimistic estimates than clinical advisor 3. In your initial submission your estimates were more aligned with clinical advisors 1&2, but during the engagement TC your estimates seemed to align more with the estimates of clinical advisor 3.

Would you therefore like to **confirm which estimates you wish to submit?**

Also, can you confirm that your estimates **include the consideration that ~50% of those in the standard care arm are likely to receive 2nd line immunotherapy upon disease progression in the NHS (as stated by yourself on the engagement TC)?**

Estimates before technical engagement TC

Overall Survival	**5 years**	**10 years**	**20 years**
Pembrolizumab combination	20%	11%	4%
Standard care	8%	3%	0%
Progression-free survival	**5 years**	**10 years**	
Pembrolizumab combination	10%	5%	4%
Standard care	3%	0%	0%

Estimates during technical engagement TC

Overall Survival	**5 years**	**10 years**	**20 years**
Pembrolizumab combination	15-20%		
Standard care	9-11%		
Progression-free survival	**5 years**	**10 years**	**20 years**
Pembrolizumab combination			
Standard care			

Could you please confirm your estimates in the box below

Confirmed estimates

Overall Survival	**5 years**	**10 years**	**20 years**
Pembrolizumab combination			
Standard care			
Progression-free survival	**5 years**	**10 years**	**20 years**
Pembrolizumab combination			
Standard care			

I am available for a call if you want to talk about this over the phone (0161 413 4125), or you can reply via NICE Docs (or both).

Thank you again for your valuable input, and we hope to hear from you as soon as possible as timelines are very restricted at this point of the appraisal process.

Best wishes,

Alan Moore
Technical Analyst
NICE
0161 413 4125

Confirmation of clinical expert estimates

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The reason this is so important is because there is high uncertainty in this appraisal and key modelling choices rest on expert clinical input. You were shown the estimates from the 3 ERG clinical advisors. ERG clinical advisors 1&2 agreed on more optimistic estimates than clinical advisor 3. In your initial submission your estimates were more aligned with clinical advisors 1&2, but during the engagement TC your estimates seemed to align more with the estimates of clinical advisor 3.

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Estimates before technical engagement TC

Overall Survival	**5 years**	**10 years**	**20 years**
Pembrolizumab combination	20%	11%	4%
Standard care	8%	3%	0%
Progression-free survival	**5 years**	**10 years**	
Pembrolizumab combination	10%	5%	4%
Standard care	3%	0%	0%

Estimates during technical engagement TC

Overall Survival	**5 years**	**10 years**	**20 years**
Pembrolizumab combination	15-20%		
Standard care	9-11%		
Progression-free survival	**5 years**	**10 years**	**20 years**
Pembrolizumab combination			
Standard care			

Could you please confirm your estimates in the box below

Confirmed estimates

Overall Survival	**5 years**	**10 years**	**20 years**
Pembrolizumab combination	18%	10%	4%
Standard care	9%	3%	0%
Progression-free survival	**5 years**	**10 years**	**20 years**
Pembrolizumab combination	10%	5%	4%
Standard care	3%	0%	0%

I am available for a call if you want to talk about this over the phone (0161 413 4125), or you can reply via NICE Docs (or both).

Thank you again for your valuable input, and we hope to hear from you as soon as possible as timelines are very restricted at this point of the appraisal process.

Best wishes,

Alan Moore
Technical Analyst
NICE
0161 413 4125

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]

Addendum: ERG critique of the company's response to NICE technical engagement

Paul Tappenden
Aline Navega Biz
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Kate Ren
School of Health and Related Research

21st March 2019

1. Introduction

In response to the NICE technical engagement process, the company provided a completed response form (29 pages), a supporting document including additional analyses (15 pages) and an updated model.[1] This addendum provides a critique of the company's technical engagement response by the ERG.

2. ERG critique of company's technical engagement response

2.1 Summary of company's updated model submitted as part of the technical engagement response

The company's revised model and analyses provided as part of their technical engagement response includes some, but not all, of the ERG's preferred analyses listed in Section 5.4.1 of the ERG report[2] (see Table 1). The company's new analyses are presented as scenario analyses rather than a revised base case.

All of the company's new scenarios include the following amendments:

- The correction of some errors identified by the ERG
- An assumption that of those standard care (SC) chemotherapy patients who go on to receive second-line treatment, 65% will receive pembrolizumab and 35% will receive atezolizumab
- An adjustment of second-line treatment duration for immunotherapy to 106 days (based on median values from KEYNOTE-010)
- The use of progression-based disease management costs (but which exclude additional PFS time for those patients receiving second-line treatment).

Using this revised model, the company presents the following scenario analyses:

- Loss of treatment effect in the pembrolizumab combination therapy group at the beginning of year 5. The ERG notes that this is incorrectly implemented in the company's new analyses based on the ERG's preferred optimistic scenario (company analyses 2c and 2d); this is because the hazard is adjusted by the log logistic function of the comparator group rather than the KM/SEER model. ERG-corrected ICERs are presented in Table 2.
- Progression-based utilities using data from the KEYNOTE-407 trial
- An analysis which combines all of these amendments.

The ERG notes that the company's new analyses: (i) do not include corrections of all errors identified by the ERG; (ii) partially implement some of the ERG's exploratory analyses and; (iii) exclude all analyses using the ERG's preferred pessimistic model. As such, the ERG believes that the company's new analyses are selective and do not fully explore the uncertainty surrounding the ICER for pembrolizumab combination therapy versus SC chemotherapy.

Table 1: ERG's exploratory analyses from the ERG report and extent to which these are incorporated within the company's new analyses

ERG's exploratory analysis / additional amendment		Included in company's revised model?	ERG comments
1: Correction of errors	Correction of OS functions for NMA comparators	Yes	-
	Correction of the HR for OS for the pembrolizumab monotherapy comparison	Yes	Not mentioned in the technical engagement response. However, this is correctly implemented in the revised model.
	Amendment of AE cost calculations	No	The revised model retains the company's original assumption that patients can experience only one AE.
	Consistent application of half-cycle correction for all treatment options	Yes	Not mentioned in the technical engagement response. However, this is correctly implemented in the revised model.
2: Use of HRQoL based on progression status	HRQoL based on progression status, using post-progression utility estimate from Khan *et al*, including additional PFS time for second-line treatment	Partially	The company presents a scenario using progression-based utilities from KEYNOTE-407. The company's analysis does not include post-progression utilities from Khan *et al*. Additional benefits of second-line PFS time are not included. This analysis is not in line with the ERG's exploratory analyses.
3: Disease management costs based on PFS/PPS	Formulae based on same assumptions as those used in exploratory analysis 2 (additional time in PFS state for those who receive second-line treatment)	Partially	The company's analyses uses progression-based management costs, but do not account for additional PFS time in patients receiving second-line treatment. This analysis is not in line with the ERG's exploratory analyses.
4: Second-line immunotherapy treatment costs doubled	Treatment duration for second-line immunotherapy was doubled	Partially	The company has amended the assumed duration of second-line treatment. However, the estimated duration is based on median values rather than means. This analysis is not in line with the ERG's exploratory analyses.
5a: Alternative PFS and OS models (optimistic)	• Pembro+chemo OS: Company's KM/log logistic model (19-week cut-point) • SC chemo OS: Company's KM/SEER model • Pembro+chemo PFS: Company's piecewise log normal model (26-week cut-point) • SC chemo PFS: Company's piecewise log normal model (26-week cut-point)	Yes	These curves are considered in the company's revised model (scenarios 2a to 2d).

ERG's exploratory analysis / additional amendment		Included in company's revised model?	ERG comments
5b: Alternative PFS and OS models (pessimistic)	• Pembro+chemo OS: ERG's log logistic model (no cut-point) • SC chemo OS: ERG's log logistic model (no cut-point) • Pembro+chemo PFS: Company's piecewise log normal model (26-week cut-point) • SC chemo PFS: Company's piecewise log normal model (26-week cut-point)	No	The company's technical engagement response does not include any analyses using the ERG's preferred pessimistic OS models.
6a and 6b: ERG-preferred analysis (optimistic and pessimistic)	Combination of ERG exploratory analyses 1-5	No	The company's revised model and scenario analyses feature several deviations from the ERG's preferred analyses.
Additional: Errors in the application of time-to-death utilities	The ERG report highlights that probability of being in the ≥360 days subgroup becomes negative at a point beyond the end of the time horizon	Yes	The company's correction introduces a further error as it produces probabilities which exceed 1.0. However, this does not affect the ICER.
Additional: Change in the 2nd line treatments for patients in SC chemotherapy group	In line with a request from the technical engagement call, the model now assumes that 65% of patients receive pembrolizumab and 35% receive atezolizumab	Yes	The company's technical engagement response[1] (page 3) erroneously states that 35% of patients receive pembrolizumab and 65% receive atezolizumab.
Additional: Treatment waning applied at 3 years post treatment discontinuation	Loss of treatment effect is applied from the beginning of year 5 (the hazard switches to that for the SC chemotherapy group)	Yes	The company has incorrectly implemented this amendment in scenarios 2c and 2d of the technical engagement response. Corrected ICERs are presented in Table 2 of this addendum.

2.2 ERG critique of key issues discussed in the company's technical engagement response

2.2.1 Issue 1: Extrapolation of overall survival

Questions from NICE:
How appropriate is the use of the SEER database to extrapolate long term survival?
Would the existing trial data from KEYNOTE 407 be more suitable to use for extrapolation?
Which statistical method is preferable to use in when estimating long term outcomes in this population? Would another parametric function be more appropriate?
What proportion of patients in the pembrolizumab combination arm would you expect to be alive at 5 and 10 years? What proportion would you expect to be progression-free at these time points?
What proportion of patients in the standard of care arm would you expect to be alive at 5 and 10 years? What proportion would you expect to be progression-free at these time points?
Is treatment with pembrolizumab combination likely to be curative in some people?

The company's technical engagement response[1] does not provide any new evidence or analyses relating to the extrapolation of outcomes for patients receiving either pembrolizumab combination therapy or standard care (SC) chemotherapy. As such, the ERG's concerns regarding the company's survival modelling have not changed; a detailed critique of this issues is provided in the ERG report[2] (Section 5.2.3, critical appraisal point 4). These concerns are summarised briefly below:

- The ERG reiterates that the expected survival of patients receiving pembrolizumab combination therapy and the expected survival of patients receiving SC chemotherapy (with a proportion of patients receiving second-line immunotherapy) are uncertain. This is largely a consequence of the short follow-up duration in IA2 of the KEYNOTE-407 trial.
- The ERG believes that none of the previous NICE technology appraisals of lung cancer treatments have involved the direct use of SEER data to inform the survival model parameters.
- The bespoke SEER dataset obtained by the company relates to three different cohorts: data from the period 2010-2014 were used to assess survival during years 1-5 of follow-up, data from 2000-2014 were used for years 6-10 of follow-up and data from 1992-2014 were used for years 11-13 of follow-up. The company's technical engagement response[1] explains that their intention was *"to make use of the most recent data available for each follow-up period."* The ERG does not believe that the company's response provides a sufficient explanation for this approach.
- The use of survival data dating back to 1992 is unlikely to reflect current practice within the NHS.
- The ERG believes that it is unlikely that any sizeable proportion of patients included in the SEER dataset could have received second-line immunotherapy.

- The applicability of the SEER dataset is further limited by differences in patient demographics, treatment pathways and healthcare systems between the US and England. Whilst two of the ERG's clinical advisors believed that the company's use of SEER data may be reasonable, they noted that caution should be exercised due to these differences.
- With respect to the relative benefit of pembrolizumab combination therapy versus SC chemotherapy, the ERG has concerns regarding the use of a relative risk (RR) as the measure for the relative treatment effect on OS, as this relates only to a specific time interval - months 7-12 in KEYNOTE-407; data from months 1-6 are excluded from the treatment effect estimate. For time-to-event data, the use of a hazard ratio (HR) would be more appropriate as this takes into account the time at which an event occurs.
- The ERG's comparison of observed OS from KEYNOTE-407 and predicted OS from the company's KM/SEER modelling approach (including the RR from KEYNOTE-407) suggests that the company's model overestimates the benefits of pembrolizumab combination therapy after 12 months (see ERG report,[2] Figure 18).
- All three of the ERG's clinical advisors believed that the company's OS extrapolation for pembrolizumab combination therapy was likely to be optimistic. None of the ERG's experts preferred the company's OS model for pembrolizumab combination therapy.
- The ERG does not believe that there is a sufficient clinical rationale to support the use of piecewise modelling for PFS or OS. The ERG's parametric survival models fitted to the whole KEYNOTE-407 dataset produced estimates of long-term OS for the SC chemotherapy group which were more plausible than those produced by the company's piecewise models and which were in line with the ERG's clinical advisors' expectations.
- The company's technical engagement response[1] states that the KEYNOTE-407 trial data alone should not be used for extrapolating long-term OS estimates. As noted in the ERG report,[2] the company's view on this matter appears to reflect a belief, in a general sense, that it is inappropriate to fit survival models to time-to-event data which are subject to administrative censoring. The ERG disagrees with this viewpoint; at the present time, the best source of information regarding the mortality hazard rates in patients with metastatic squamous NSCLC receiving first-line pembrolizumab combination therapy or SC chemotherapy (including currently available second-line immunotherapy) is the observed period of KEYNOTE-407.

In addition to the concerns raised in the ERG report,[2] the ERG also makes the following observations:

- The company's technical engagement response[1] states that the PFS and OS estimates obtained by the NICE technical team broadly agree with estimates from two of the ERG's clinical advisors. However, the ERG notes that the question that NICE asked their clinical expert does not mention the use of second-line pembrolizumab as part of the SC chemotherapy pathway;

as such, it is unclear whether NICE's expert took account of this when providing their estimates of OS for the comparator group. One of the ERG's clinical advisors suggested a more pessimistic expectation of OS for pembrolizumab combination therapy compared with the other two advisors. The ERG notes that the difference between the mean estimates of OS for SC chemotherapy from the ERG's optimistic and pessimistic scenarios is fairly small (1.97 versus 2.17 years); however, this does impact on the ICER and may influence judgements regarding whether NICE's End of Life (EoL) criteria are met.

- The company's technical engagement response[1] cites a paper by Bullement *et al*[3] which suggests that *"manufacturer reported estimates for long term OS of IO drugs tend to underestimate the results once longer term data cuts are available if anything."* The ERG notes that three of the authors of this paper are employed by the company, one of whom also authored the company's technical engagement response. The ERG considers that the conclusions drawn from this paper are entirely unrelated to whether the company's current OS estimates for pembrolizumab combination therapy, estimated using the KM/SEER data and a treatment effect from KEYNOTE-407, are plausible. The ERG and its clinical advisors believe that the incremental OS gain predicted by the company's base case model is likely to be optimistic.
- Whilst there is considerable uncertainty regarding long-term OS gains, neither the CS[4] nor the company's technical engagement response[1] provide an adequate exploration of this uncertainty. The CS includes two sensitivity analyses using a log normal and an exponential OS model (assuming a 19 week cut-point); the company's technical engagement response considers only the company's KM/SEER approach and the ERG's optimistic scenario.[2] The ERG's exploratory analyses show that the choice of curve may have a marked impact on the ICER for pembrolizumab combination therapy. All of the company's piecewise parametric models produced ICERs which are higher than the company's base case model (see ERG report,[2] Table 37). All of the ERG's parametric models produced ICERs which are higher than the company's base case model (see ERG report,[2] Table 45).
- The company's technical engagement response[1] states that clinical experts consulted by the company *"suggested that if a patient were to survive to 18 years post diagnosis then it would be reasonable to assume their mortality risk was that of the general population and that this could be possible for a proportion of patients."* The company's response does not provide any details regarding whether these clinicians were asked whether it is plausible that 9.9% of patients receiving pembrolizumab combination therapy will be alive and cured after 18 years.

2.2.2 Issue 2: Place of pembrolizumab combination therapy in the treatment pathway

Questions from NICE:
Would it be more appropriate to use pembrolizumab combination therapy as a first line treatment option for patients who do not have strong PD-L1 expression (TPS <1% and 1-49% subgroups), or to reserve immunotherapy as a treatment option at second-line?
Would it be more appropriate to use pembrolizumab as first-line combination therapy or as monotherapy for patients with PD-L1 strong expression (TPS >50%)?

The company's technical engagement response[1] provides discussion to support their intended position in the treatment pathway from the original CS as a first-line treatment for populations with and without strong PD-L1 expression. This includes presentation of evidence from KEYNOTE-407 (Table 3-5 of the evidence supporting document), and reference to a review article examining the uptake of second-line treatment in NSCLC.[5]

- The company reiterates that pembrolizumab combination therapy was effective over control regardless of PD-L1 status. Table 3 of the evidence supporting document describes that the median OS was not reached in the PD-L1 ≥50% subgroup in either the pembrolizumab combination or control groups indicating some correlation between higher PD-L1 status and OS. The KM curves separated earlier with increasing PD-L1 tumour proportion score (TPS) indicating that treatment response to pembrolizumab combination therapy appears to occur earlier with in patients with higher PD-L1 TPS at baseline. As described in the ERG report[2] (Section 4.2.2) PD-L1 expression may be altered by chemotherapy.
- The company emphasises using Table 5 of the evidence supporting document that utilisation of second-line treatment after discontinuing from study treatment in KEYNOTE-407 (ASaT population) due to progressive disease, adverse event and physician decision was lower in the control arm compared with the pembrolizumab combination arm. The company states that the results imply that these patients were not well enough to receive further second-line therapy. They further state that if immunotherapy was to be reserved as a second-line option, the pool of patients who would could benefit from immunotherapy would be smaller. The ERG reiterates that the absolute number of treatment discontinuations was higher for pembrolizumab combination therapy (as described in Section 4.2.3 of the ERG report).
- The reference provided by the company that examined use of subsequent lines of treatment in advanced NSCLC (Davies *et al* 2017[5]) does not empirically demonstrate a benefit of receiving first-line versus second-line immunotherapy. This "qualitative data synthesis" of observational studies only indicates that between one-third to one-half of those who received first-line treatment also received second-line therapy. Whilst reasons for not receiving later lines of therapy are stated to include "poor PS and poor response to first-line therapy", alternative reasons and the proportion of responders/non-responders by treatment line are not provided.

2.2.3 Issue 3: Use of subsequent-line treatments

Questions from NICE:
What percentage of people, who receive first-line standard chemotherapy treatment, would be expected to receive second-line immunotherapy following disease progression?
How long would these people be expected to be treated with second-line immunotherapy?
Which second-line immunotherapies would be used and in what proportions?

The company's technical engagement response[1] includes the following adjustments to the model:

(i) Of the [redacted] of patients in the comparator group who are assumed to receive second-line treatment, 65% are assumed to receive pembrolizumab monotherapy, and the remaining 35% are assumed to receive atezolizumab monotherapy. The company's revised model assumes that no patients in the SC chemotherapy group receive chemotherapy or nivolumab as a second-line treatment.

(ii) Treatment duration for patients receiving these second-line treatments is assumed to be 15.1 weeks (106 days). This estimate is reported to have been based on the median exposure time from KEYNOTE-010[6] and TA520.[7]

With respect to these amendments, the ERG notes the following:

- The company's revised model and scenario analyses do not include any amendment to the probability of receiving second-line treatment in the SC comparator group. The revised model assumes that a different mix of second-line treatments are available compared with the company's original base case model.
- The company's model does not include a causal link between the probability of receiving second-line immunotherapy and OS. As such, increasing the proportion of patients receiving second-line immunotherapy increases the total costs for the comparator group, but has no effect on health outcomes. As a consequence, this improves the ICER for pembrolizumab combination therapy. The ERG believes that the increased use of second-line immunotherapy would improve OS for the SC chemotherapy group; this improvement is not captured in the analyses. Consequently, the company's revised analyses are likely to favour the pembrolizumab combination therapy group and should be approached with caution.
- The ERG could not locate treatment exposure time for atezolizumab from the committee papers for TA520.[7]
- The ERG believes that the company's use of median exposure time is likely to underestimate treatment duration. Within TA428,[8] PFS was used as a proxy for treatment

duration; the (discounted) mean PFS sojourn time was approximately 7.3 months. This is considerably higher than the company's median estimate of 106 days (3.5 months).

- Table 3 presents additional analyses undertaken by the ERG based on the ERG's preferred analyses (company's original treatment duration doubled, 65% receive pembrolizumab, 35% receive atezolizumab). This amendment reduces the ICERs of pembrolizumab combination therapy by approximately £2,000 to £3,000 per QALY gained.

2.2.4 Issue 4: Treatment effect after discontinuation of pembrolizumab treatment

Questions from NICE:
What is the most clinically plausible assumed treatment effect for pembrolizumab once treatment with this drug has stopped?
Is there any additional evidence which could be used to inform the duration of treatment effect?

The company's technical engagement response[1] includes scenarios in which the treatment effect is removed at the beginning of year 5; this scenario was also presented in the CS. As noted above, the company's implementation of this analysis using the ERG's optimistic scenario (company's scenarios 2c and 2d) is incorrectly implemented; corrected ICERs are presented in Table 2. The company's response states *"there is no data to suggest a waning of treatment effect."* The company has not presented any new evidence relating to the duration over which the treatment effect may apply; this remains a key area of uncertainty. A critique of this issue is presented in the ERG report (Section 5.2.3, critical appraisal point 5). The ERG highlights that:

- The clinical advisors to the ERG agreed that the company's base case assumption of a lifetime treatment effect was likely to be overly optimistic.
- Removing the treatment effect at earlier timepoints has the propensity to substantially increase the ICER for pembrolizumab combination therapy (see ERG report,[2] Table 36).
- The ERG's clinical advisors noted considerable uncertainty relating to the duration of treatment response and its impact on OS outcomes.

2.2.5 Issue 5: Network meta-analysis (NMA) for comparators

Questions from NICE:
Do the NMAs and indirect treatment comparisons provide robust enough evidence for decision making? Are the trials included in the NMAs and ITCs generalizable to the UK?
Should the trials including an ECOG performance status of 2 be excluded or adjusted for to minimise the risk of bias?
Are the various standard chemotherapy regimens considered to be broadly similar?

The company's technical engagement response[1] highlights that clinical opinion suggests that all first-line treatments are comparable. This view is consistent with clinical advice received by the ERG (see ERG report,[2] Section 5.2.3, critical appraisal point 2); the ERG therefore has no further comments on this issue.

2.2.6 Issue 6: Health-related quality of life measurement

Questions from NICE:
Are time to death utilities appropriate to capture health-related quality of life (HRQoL) within this population? Would health utilities based on progression status be more suited for use?
How robust are the health utilities estimates directly collected within KEYNOTE 407? Should utility values from the literature be used instead of utilities collected within KEYNOTE 407? How valid are the utility values used by the ERG in its analyses (from Khan et al)?

The company's technical engagement response[1] does not provide any new evidence which justifies their use of the time-to-death utility approach using data from KEYNOTE-407. A critique of the company's approach is contained in the ERG report,[2] (Section 5.2.3, critical appraisal point 7). The ERG's concerns have not changed. The ERG notes the following key points:

- The ERG's main concern is that within KEYNOTE-407, EQ-5D assessments for progressed patients were undertaken only shortly after disease progression was established (at most, 30 days later). As such, the data from KEYNOTE-407 are likely to be subject to informative censoring. Irrespective of whether a time-to-death approach or progression-based utility approach is taken, the estimates obtained from this data source are likely to be biased and neither method can resolve this problem without the use of external data. This is why the ERG believes that it is more appropriate to use progression-based utilities and why an external source is required to inform the post-progression utility.
- As explained in the ERG report,[2] the ERG believes that the TOPICAL trial (Khan *et al*[9]) represents a reasonable alternative source of post-progression utility because: (i) this trial included collection of HRQoL data in progressed patients; (ii) HRQoL was measured using the EQ-5D, and (iii) few patients in the placebo group received active therapy after disease progression, hence the estimate is unlikely to be contaminated by post-progression treatments.
- The company's technical engagement response states that they used data from KEYNOTE-407 because this is in line with the NICE Reference Case.[10] The ERG notes that using Khan *et al* is also in line with the NICE Reference Case and this source has been used to inform post-progression utility estimates in previous NICE appraisals (e.g. TA411 - necitumumab for NSCLC).

- Whilst the company argues that the patient populations recruited into Khan *et al* and KEYNOTE-407 are different, the parameter required for the model (EQ-5D utility in patients with progressed disease) does not relate to the randomised populations of these studies.
- The company has presented an analysis using the post-progression utility from KEYNOTE-407. This analysis differs from the ERG's exploratory analyses, as it does not consider any additional progression-free time for patients at second-line. As noted above, the estimates derived from KEYNOTE-407 are likely to be biased due to informative censoring.
- The company's technical engagement response[1] attempts to justify the high utility values for patients in the time-to-death approach, suggesting that it may be reasonable for the model to include utility values for patients with metastatic NSCLC which are higher than those for the general population. The company's technical engagement response does not provide any evidence to support this argument and the ERG believes that this viewpoint is neither logically consistent nor reasonable.

2.2.7 Issue 7: End of life criteria

Questions from NICE:
Under standard care, is the life expectancy of adults with metastatic squamous non-small-cell lung cancer (NSCLC) more than 24 months?
Does pembrolizumab combination therapy extend life for more than 3 months compared with standard care?

The company's technical engagement response[1] provides some further explanation regarding their belief that pembrolizumab meets NICE's EoL criteria. As noted in the ERG report (Section 6), there is uncertainty regarding whether these criteria are met: under the ERG's preferred optimistic scenario, the criteria were met, whilst under the ERG's preferred pessimistic scenario, the criteria were not met. The ERG believes that owing to the uncertainty regarding the expected survival duration for patients receiving SC chemotherapy (with a proportion of patients also receiving second-line immunotherapy), it is unclear whether pembrolizumab combination therapy meets NICE's EoL criteria. The ERG's exploratory analyses indicate that across the full range of ERG-fitted OS models, the EoL criteria are met in the majority of scenarios; however, the ICER for pembrolizumab combination therapy remains above £50,000 per QALY gained across all of these scenarios (see ERG report,[2] Table 45).

With respect to the company's technical engagement response, the ERG notes the following additional observations:

- The company's response states: *"The company submitted model predicts a median OS for the SoC arm of 11.5 months using the company's preferred KM/SEER extrapolation. This suggests*

that the prediction of the model is broadly in line with the observed data." The ERG notes that this is unsurprising as the observed KM curves are used for the first 12 months of the model.

- The company's response highlights that the NICE technical report[11] suggests that OS for the SC chemotherapy group is likely to have been overestimated using SEER. The ERG believes that it is more likely that OS is underestimated in this group (due to the absence of second-line immunotherapy).
- The company's response reports median OS estimates from other trials in patients with NSCLC. The ERG believes that the consideration of median survival is not appropriate for determining average life expectancy. In instances in which treatments are expected to lead to long-term survival in a proportion of patients, median and mean values will diverge.
- The company's response states *"it should be considered that approximately 50% of the patients who are treated with first line treatment are actually receiving a second line treatment therefore looking the actual survival of patients with squamous population is expected to be much lower than 24 months."* The ERG notes that second-line immunotherapy use is part of the standard pathway for NSCLC and should be included in any estimates of expected survival for these patients.

2.2.8 Issue 8: Cancer Drugs Fund

Questions from NICE:
Is there further data being collected that could reduce uncertainty surrounding longer term effectiveness and health outcomes in this population?
When will these additional data become available?
How suitable is the technology for use in the Cancer Drugs Fund (CDF)?

The company's technical engagement response[1] notes that the final analysis of KEYNOTE-407 is expected in [redacted] The ERG believes that these additional data from KEYNOTE-407 will help to resolve uncertainty surrounding long-term PFS and OS estimates.

3. Additional analyses undertaken by the ERG

Table 2: Results of company's analysis versus ERG corrected analysis, Scenarios 2c and 2d

Option	Company's results							ERG's corrected results						
	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Overall population														
Scenario 2c														
Pembrolizumab combination	3.79	2.32	£65,590	1.82	1.05	£37,102	**£35,185**	3.53	2.21	£64,583	1.56	0.95	£36,095	**£38,182**
SC chemotherapy	1.97	1.27	£28,488	-	-	-	-	1.97	1.27	£28,488	-	-	-	-
Scenario 2d														
Pembrolizumab combination	3.79	2.19	£65,590	1.82	0.99	£37,102	**£37,656**	3.53	2.10	£64,583	1.56	0.89	£36,095	**£40,388**
SC chemotherapy	1.97	1.20	£28,488	-	-	-	-	1.97	1.20	£28,488	-	-	-	-
PD-L1 TPS ≥50% subgroup														
Scenario 2c														
Pembrolizumab combination	4.42	2.60	£66,925	2.41	1.31	£38,953	**£29,768**	3.57	2.23	£63,238	1.57	0.95	£35,266	**£37,248**
Pembrolizumab mono	4.26	2.50	£72,634	-	-	-	**Dominated**	3.46	2.16	£69,121	-	-	-	**Dominated**
SC chemotherapy	2.00	1.29	£27,972	-	-	-	-	2.00	1.29	£27,972	-	-	-	
Scenario 2d														
Pembrolizumab combination	4.42	2.34	£66,925	2.41	1.11	£38,953	**£35,121**	3.57	2.05	£63,238	1.57	0.82	£35,266	**£43,042**
Pembrolizumab mono	4.26	2.19	£72,634	-	-	-	**Dominated**	3.46	1.91	£69,121	-	-	-	**Dominated**
SC chemotherapy	2.00	1.24	£27,972	-	-	-	-	2.00	1.24	£27,972	-	-	-	-

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted*

Table 3: Results of ERG-preferred analyses with/without change in second-line treatment regimens, pembrolizumab combination therapy versus carboplatin plus paclitaxel/nab-paclitaxel

Option	ERG's optimistic scenario							ERG's pessimistic scenario						
	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Overall population														
ERG exploratory analysis 6 - ERG preferred analysis (original)														
Pembrolizumab combination	3.94	2.17	£66,008	1.98	1.01	£36,387	**£35,981**	3.23	1.91	£62,832	1.06	0.65	£32,050	**£49,473**
SC chemotherapy	1.97	1.16	£29,621	-	-	-	-	2.17	1.26	£30,782	-	-	-	-
ERG exploratory analysis 6 - ERG preferred analysis, including change in second-line treatment														
Pembrolizumab combination	3.94	2.17	£66,008	1.98	1.01	£34,128	**£33,631**	3.23	1.91	£62,832	1.06	0.65	£29,782	**£45,680**
SC chemotherapy	1.97	1.16	£31,879	-	-	-	-	2.17	1.26	£33,050	-	-	-	-
PD-L1 TPS ≥50% subgroup														
ERG exploratory analysis 6 - ERG preferred analysis (original)														
Pembrolizumab combination	4.02	2.11	£64,708	2.02	0.91	£35,519	**£39,193**	3.72	2.01	£63,425	-	-	-	**Dominated**
Pembrolizumab mono	3.85	2.06	£67,519	-	-	-	**Dominated**	3.56	1.96	£66,382	-	-	-	**Dominated**
SC chemotherapy	2.00	1.20	£29,189	-	-	-	-	4.01	2.03	£38,907	-	-	-	**Dominating**
ERG exploratory analysis 6 - ERG preferred analysis, including change in second-line treatment														
Pembrolizumab combination	4.02	2.11	£64,708	2.02	0.91	£33,269	**£36,592**	3.72	2.01	£63,425	-	-	-	**Dominated**
Pembrolizumab mono	2.00	1.20	£31,438	-	-	-	**Dominated**	3.56	1.94	£66,382	-	-	-	**Dominated**
SC chemotherapy	3.85	2.04	£67,519	-	-	-	-	4.01	2.02	£41,233	-	-	-	**Dominating**
PD-L1 TPS 1-49% subgroup														
ERG exploratory analysis 6 - ERG preferred analysis (original)														
Pembrolizumab combination	3.60	2.13	£69,348	1.59	0.96	£39,146	**£40,767**	3.12	1.91	£67,684	1.03	0.70	£37,023	**£52,680**
SC chemotherapy	2.02	1.17	£30,203	-	-	-	-	2.09	1.21	£30,661	-	-	-	-
ERG exploratory analysis 6 - ERG preferred analysis, including change in second-line treatment														
Pembrolizumab combination	3.60	2.13	£69,348	1.59	0.96	£36,879	**£38,244**	3.12	1.91	£67,684	1.03	0.71	£34,753	**£49,149**
SC chemotherapy	2.02	1.16	£32,469	-	-	-	-	2.09	1.20	£32,931	-	-	-	-

Option	ERG's optimistic scenario							ERG's pessimistic scenario						
	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS <1% subgroup														
ERG exploratory analysis 6 - ERG preferred analysis (original)														
Pembrolizumab combination	3.83	2.03	£64,296	1.98	0.93	£32,126	**£34,392**	3.29	1.85	£61,898	1.88	0.93	£31,918	**£34,239**
SC chemotherapy	1.84	1.10	£32,170	-	-	-	-	1.40	0.92	£29,980	-	-	-	-
ERG exploratory analysis 6 - ERG preferred analysis, including change in second-line treatment														
Pembrolizumab combination	3.94	2.03	£64,296	1.98	0.94	£30,316	**£32,343**	3.29	1.85	£61,898	1.88	0.93	£30,125	**£32,245**
SC chemotherapy	1.97	1.10	£33,980	-	-	-	-	1.40	0.92	£31,772	-	-	-	-

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year

** undiscounted; all patients receive only nivolumab (in the original model) or atezolizumab (in the revised model), since pembrolizumab is only available as 2nd line for patients PD-L1 TPS>1%.*

3. References

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