Single Technology Appraisal

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Regeneron:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Roy Castle Lung Cancer Foundation
   b. British Thoracic Oncology Group

4. **External Assessment Report** prepared by Newcastle NIHR TAR Team

5. **External Assessment Report – factual accuracy check**

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

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Document B

Company evidence submission

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Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike's information criterion
ALK	Anaplastic lymphoma kinase
ALT	Alanine transferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BIC	Bayesian information criterion
BRAF V600E	v-raf murine sarcoma viral oncogene homolog B1
BSA	Body surface area
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CR	Complete response
CrI	Credible interval
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire
EORTC QLQ-L13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer
EMA	European Medicines Agency
GHS	Global health status
HERC	Health Economics Research Centre
HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Healthcare resource utilisation
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
IO	Immunotherapy
IPD	Individual patient data
IQR	Interquartile range
IRC	Independent review committee
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
laBCC	Locally advanced basal cell carcinoma
laCSCC	Locally advanced cutaneous squamous cell carcinoma
MAE	Mean absolute error
mBCC	Metastatic basal cell carcinoma
mCSCC	Metastatic cutaneous squamous cell carcinoma
MET	Mesenchymal-epithelial transition factor
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed models for repeated measures
NMA	Network meta-analysis
NSCLC	Non-small-cell lung cancer
NTRK	Neurotrophic tyrosine receptor kinase
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival

OWSA	One-way sensitivity analysis
PD	Progressive disease
PD-1	Programmed cell death receptor 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PH	Proportional hazards
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised clinical trial
RET	Rearranged during transfection
RMSE	Root mean squared error
ROS-1	Ros proto-oncogene 1
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
SE	Standard error
SITC	Society for Immunotherapy of Cancer
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
ToT	Time on treatment
TTD	Time to treatment discontinuation

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. Table 1 shows the decision problem addressed in the submission.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated locally advanced (which is not a candidate for definitive chemoradiation) or metastatic NSCLC which expresses PD-L1 on 1% or more of tumour cells and has no EGFR, ALK or ROS-1 genetic alterations	Adults with untreated locally advanced (which is not a candidate for definitive chemoradiation) or metastatic NSCLC which expresses PD-L1 on 1% or more of tumour cells and has no EGFR, ALK or ROS-1 genetic alterations	N/A
Intervention	Cemiplimab with chemotherapy	Cemiplimab with chemotherapy	N/A
Comparator(s)	For people with squamous NSCLC whose tumours express PD-L1 on 1 to 49% of tumour cells: • Platinum doublet chemotherapy • Pembrolizumab with carboplatin and paclitaxel For people with squamous NSCLC whose tumours express PD-L1 on 50% or more of cells: • Platinum doublet chemotherapy • Pembrolizumab monotherapy • Atezolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel (for people in need of urgent clinical intervention) For people with non-squamous NSCLC whose tumours express PD-L1 on 1 to 49% of tumour cells:	For people with squamous and non-squamous NSCLC whose tumours express PD-L1 on greater than 1% of tumour cells: • Pembrolizumab + chemotherapy per NHS England commissioning policies (1)	Regeneron considers pembrolizumab + chemotherapy (which has >80% market share among NICE-recommended immunotherapy (IO) + chemotherapy options across histologies and PD-L1 expression levels ≥1% (2)) to be the only relevant comparator for this appraisal: • Feedback from UK clinical expert lung oncologists consulted during development of this submission confirmed that patients offered IO + chemotherapy comprise a patient group who are clinically distinct from those who would typically be offered chemotherapy alone because they are not considered suitable for IO, or from those who would typically be offered an IO monotherapy instead of in combination with chemotherapy • The only other NICE-recommended IO given in combination with chemotherapy is atezolizumab

	• Pembrolizumab with pemetrexed and platinum chemotherapy • Atezolizumab with bevacizumab, carboplatin and paclitaxel • Pemetrexed with platinum doublet chemotherapy For people with non-squamous NSCLC whose tumours express PD-L1 on 50% or more of cells: • Pembrolizumab with pemetrexed and platinum chemotherapy • Pembrolizumab monotherapy • Atezolizumab monotherapy • Pemetrexed with platinum doublet chemotherapy		(TA584), which is available for use only in people with non-squamous disease and PD-L1 1-49%, and is not commonly used in UK clinical practice (having approximately 8% of market share in that population (2)) • UK clinical expert lung oncologists have confirmed that pembrolizumab + chemotherapy is the relevant comparator that would be displaced by use of cemiplimab + chemotherapy Overall, cemiplimab + chemotherapy will primarily act as an alternative to the current standard of care for the first-line treatment of patients in the PD-L1 ≥1%, any histology population for which it is licensed (i.e., pembrolizumab + chemotherapy)
Outcomes	• Progression-free survival • Response rates • Overall survival • Adverse effects of treatment • Health-related quality of life	• Progression-free survival • Response rates • Overall survival • Adverse effects of treatment • Health-related quality of life	N/A
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. 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	A cost-comparison analysis (assuming equivalent clinical outcomes) will be included as an alternative base case alongside a cost-utility analysis	A key challenge associated with conducting a cost-utility analysis to address the relevant decision problem on the cost-effectiveness of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy is the lack of head-to-head RCT evidence. As expected, there were limitations in conducting the NMA (due to inherent

	outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		limitations in the evidence base and a lack of published data for the relevant comparator), and the results are associated with uncertainty as reflected in wide credible intervals. However, all the available evidence from the trial data, previously published NMA, and the Company NMA points to a conclusion of similar efficacy. This view is shared by UK clinical experts experienced in the use of IO therapy in NSCLC, and by CADTH and PBAC. On this basis, a cost-utility analysis has been provided per the NICE scope and reference case, but a cost comparison analysis has also been provided to facilitate pragmatic decision-making. This pragmatic cost comparison approach was accepted previously by NICE (e.g. in TA705) and by both CADTH and PBAC. As described in more detail in Section B.3, Regeneron believes that currently, the justification for modelling equivalent efficacy for cemiplimab + chemotherapy and pembrolizumab + chemotherapy is stronger than the justification for modelling any differences in efficacy: • Cemiplimab and pembrolizumab have the same mechanism of action • There is no published evidence suggesting differences in OS or PFS between cemiplimab and pembrolizumab • Only cemiplimab + chemotherapy and pembrolizumab + chemotherapy have and NCCN 'preferred'

			recommendation in advanced/metastatic NSCLC • UK clinical expert lung oncologists noted similarity in efficacy between the two treatments As stated above, a pragmatic cost-comparison approach has previously been accepted by other international HTA bodies.
Subgroups to be considered	• Histology • PD-L1 status • Disease stage • Newly diagnosed or recurrent after surgery metastatic disease	Four subgroups will be considered, based on histology and PD-L1 levels to reflect the current UK treatment pathway: • Squamous, PD-L1 1-49% • Squamous, PD-L1 ≥50% • Non-squamous, PD-L1 1-49% • Non-squamous, PD-L1 ≥50%	The submission will not include subgroup analyses by disease stage or by newly diagnosed or recurrent after surgery metastatic disease for the following reasons: <u>Disease stage</u> In the UK, the Blueteq protocol (i.e. NHS England commissioning policy) permits treatment of patients with locally advanced NSCLC who are not candidates for definitive chemoradiation with pembrolizumab, despite pembrolizumab not having a marketing authorisation in locally advanced disease (1). These patients are therefore managed in the same way as those with metastatic disease, so subgroup analysis by disease stage lacks relevance to UK clinical practice and treatment decisions. Feedback from UK clinical expert lung oncologists suggested that neither clinical outcomes nor costs would be expected to be meaningfully different for patients with locally advanced disease (not eligible for

			definitive chemoradiation) versus metastatic disease. Although subgroup analysis by disease stage was planned in the overall population of the EMPOWER-Lung 3 RCT, the small number of patients in the study who were in the licensed population (i.e. PD-L1 ≥1%) with locally advanced NSCLC precludes robust subgroup analysis. <u>Newly diagnosed or recurrent after surgery metastatic disease</u> Feedback from UK clinical expert lung oncologists suggested that neither clinical outcomes nor costs would be expected to be meaningfully different for people who have versus those who have not undergone prior surgery for NSCLC.

B.1.2 Description of the technology being evaluated

Cemiplimab is a fully human IgG4 monoclonal antibody developed by Regeneron and approved in the UK for multiple solid tumours which binds to the programmed cell death protein-1 (PD-1) receptor and blocks its interaction with its ligands, PD-L1 and PD-L2 (3). In 2015, Regeneron and Sanofi entered into license and collaboration agreement for cemiplimab whereby Sanofi was solely responsible for commercialisation outside the US. In July 2022, Regeneron re-acquired ex-US commercialisation rights from Sanofi and is now solely responsible for cemiplimab commercialisation worldwide (4).

Cemiplimab in combination with platinum-based chemotherapy was granted EMA marketing authorisation in NSCLC on 29 March 2023, followed by MHRA marketing authorisation on 2 February 2024 (EU reliance route). The summary of product characteristics and the European Public Assessment Report for the Type II variation to include cemiplimab in combination with chemotherapy for treatment of NSCLC can be found in Appendix C.

Table 2 Technology being evaluated

UK approved name and brand name	Cemiplimab (Libtayo®) This submission is for cemiplimab in combination with platinum-based chemotherapy.
Mechanism of action	Cemiplimab is a fully human IgG4 monoclonal antibody that binds to the programmed cell death protein-1 (PD-1) receptor on the surface of T cells and blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2. This inhibition of the PD-1 pathway enhances the T cell mediated immune response, leading to T cell activation and proliferation against tumour cells (3).
Marketing authorisation/CE mark status	Cemiplimab in combination with platinum-based chemotherapy was granted EMA marketing authorisation in NSCLC on 29 March 2023, followed by MHRA marketing authorisation on 2 February 2024 (EU reliance route).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Cemiplimab in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in

	≥1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have: • locally advanced NSCLC that is not suitable for definitive chemoradiation, or • metastatic NSCLC Cemiplimab is also indicated as monotherapy for treatment of adult patients with: • NSCLC expressing PD-L1 (in ≥50% of tumour cells), with no with no EGFR, ALK or ROS1 aberrations, who have locally advanced NSCLC that is not suitable for definitive chemoradiation, or metastatic NSCLC (MHRA approval September 2021) • metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation (MHRA approval August 2022)[a] • locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI) (MHRA approval September 2021) • recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy (MHRA approval April 2023) CSCC is the only other indication for which cemiplimab has been evaluated (and was subsequently recommended as an option for) by NICE to date (TA802) (5)
Method of administration and dosage	<u>Dosing</u> The recommended dose of cemiplimab is 350 mg every 3 weeks (Q3W). Treatment may be continued until disease progression or unacceptable toxicity. The SmPC states that treatment may be continued until disease progression or unacceptable toxicity. However, a 2-year stopping rule is anticipated in line with guidance for pembrolizumab + chemotherapy (TA683 and TA770) No dose reductions are recommended; dosing delay or discontinuation may be required based on individual safety and tolerability (see SmPC for full details). No dose adjustment is recommended for elderly patients, or for patients with renal impairment or mild or moderate hepatic impairment. Cemiplimab has not been studied in patients with severe hepatic impairment.

	Administration Cemiplimab is administered as an intravenous (IV) infusion over 30 minutes. Other medicinal products should not be co-administered through the same IV line.
Additional tests or investigations	A PD-L1 test is required to confirm suitability for treatment; however, because this is done as part of routine practice for all patients to inform treatment selection, Regeneron does not anticipate any additional testing/concomitant medication, or associated costs, for the NHS beyond routine clinical practice. The PD-L1 assay used in EMPOWER LUNG-3 (Ventana SP263) differed from that used in the pembrolizumab KEYNOTE studies (22C3 pharmDX platform) and commonly used in NHS labs (6, 7). However, there is high concordance across the two assays and the Society for Immunotherapy of Cancer (SITC) considers them to be “interchangeable” (8).
List price and average cost of a course of treatment	£4650 per vial The average cost of treatment at list price with cemiplimab + chemotherapy in the first year is £61,350.89
Patient access scheme (if applicable)	A simple PAS discount for cemiplimab was approved as a condition of the previous NICE recommendation for cemiplimab in patients with cutaneous squamous cell carcinoma (TA802). Regeneron is entering commercial discussions with NHS England with regard to the indication under consideration as part of this TA for people with NSCLC

[a]In May 2024, cemiplimab moved from a score of 3 to 4 on the ESMO Magnitude of Benefit Scale, which implies an improvement in ESMO’s perception of clinical benefit from moderate to high.

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; NSCLC, non-small cell lung cancer; PD-1, programmed cell death receptor 1; ROS1, ROS proto-oncogene 1; SmPC, summary of product characteristics

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

Key points

- Lung cancer is the leading cause of cancer-related deaths in the UK
- NSCLC accounts for 85% to 90% of lung cancers
- It is estimated that there were 37,259 cases of lung cancer in England and Wales in 2023. Of these, 34,129 were NSCLC
- In England, pembrolizumab + chemotherapy is the current standard of care IO + chemotherapy option for people with locally advanced (not eligible for definitive chemoradiation)/metastatic NSCLC with PD-L1 levels ≥1%. However, based on drug protocols evaluated in the registrational KEYNOTE studies, the Blueteq protocols (i.e. NHS England commissioning policy) for pembrolizumab + chemotherapy (1):
    - require people with squamous disease to be “fit for AUC6 carboplatin”
    - only list pemetrexed-containing regimens for people with non-squamous disease
- Clinical expert lung oncologists who routinely treat NHS patients in England explained that:
    - higher-dose (AUC6) carboplatin is associated with significant incremental toxicity relative to lower-dose (AUC5) carboplatin e.g. thrombocytopenia
    - pemetrexed is associated with significant toxicities and may not be suitable for all people with non-squamous disease (see Section B.1.3.8)
    - the option to initiate treatment with carboplatin at a lower dose for people with squamous disease (AUC5), and to use an alternative to pemetrexed for people with non-squamous disease (e.g. paclitaxel), alongside an IO agent would be “helpful” and “useful”

- this flexibility may benefit, for example, older patients, those with renal, cardiac or hepatic impairment, or those with a high comorbidity burden.

- Cemiplimab +chemotherapy offers this flexibility, as the EMPOWER-Lung 3 protocol gave investigators the option to use:
  - carboplatin AUC5 as an alternative to the higher dose of carboplatin (AUC6) in squamous patients
  - a pemetrexed-free option (with paclitaxel + carboplatin), in non-squamous patients
- In addition, pembrolizumab + chemotherapy is not licensed for patients with locally advanced disease who are not eligible for definitive chemoradiation
- There is therefore an unmet need for an alternative treatment option that:
  - gives clinicians greater flexibility to tailor chemotherapy treatment according to individual patient characteristics, needs, and preferences;
  - is approved by MHRA for use in patients with locally advanced disease who are not eligible for definitive chemoradiation.

B.1.3.1 Overview of NSCLC

Lung cancer is the third most common cancer and the leading cause of cancer-related deaths in the UK (9). It is broadly classified into two main types based on the cell type in which the cancer originated: NSCLC (which represents approximately 85% to 90% of diagnoses) and small cell lung cancer (SCLC), which accounts for the remaining 10% to 15% of cases (10).

NSCLC is further categorised into squamous cell carcinoma and non-squamous cell carcinoma (which includes adenocarcinoma and large cell carcinoma). Non-squamous cell carcinoma is more common (representing approximately 70 to 75% of NSCLC cases in the UK) (10).

B.1.3.2 Pathophysiology

The pathogenesis of lung cancer is complex and not fully understood, although there appear to be specific pathogenic patterns associated with each histologic type of

NSCLC (11). Genes involved in the pathogenesis of NSCLC produce proteins that are involved in cell growth, differentiation, cell cycle processes, apoptosis, angiogenesis, tumour progression and immune regulation.

Over the past decade, genetic alterations or oncogenic driver mutations have also been implicated in the pathogenesis of NSCLC (12, 13). Targeted therapies may be recommended based on the identification of a driver oncogene, such as *EGFR*, *ALK*, *ROS1*, *BRAF V600E*, *NTRK*, *MET*, *RET* and *KRAS* (14).

B.1.3.3 PD-L1 status

Programmed death-ligand 1 (PD-L1) is a protein that is involved in suppressing the body's immune response to cancer. NSCLC cells express elevated levels of PD-L1 on their surface (15). PD-L1 binds to the programmed death-1 (PD-1) receptor, which is expressed predominantly on activated T-cells; this binding prevents the immune response.

PD-L1 status helps determine whether a patient is suitable for treatment with immune checkpoint inhibitors (such as cemiplimab) that block the interaction between PD-L1 and PD-1, allowing the immune system to recognise and attack cancer cells. PD-L1 expression is a potential treatment effect modifier: as seen in clinical trials of immunotherapies (IOs) in NSCLC, the response rate increased with increasing PD-L1 expression, although benefit was seen across all PD-L1 expression subgroups (16, 17).

PD-L1 status is assessed using an immunohistochemistry (IHC) biomarker assay and is reported as the percentage of tumour cells expressing PD-L1 on their surface:

- <1% = negative expression
- 1 – 49% = low expression
- ≥50% = high expression

In England and Wales, the 22C3 (Dako) IHC assay is most commonly used to determine PD-L1 status in NHS labs (6, 7). The Ventana SP263 assay was used in the registrational randomised clinical trial (RCT) for cemiplimab + chemotherapy described in this submission (EMPOWER-Lung 3; Section B.2.1), whereas the 22C3

assay was used in the registrational studies of the relevant comparator for this appraisal, i.e. pembrolizumab + chemotherapy (KEYNOTE-189 and KEYNOTE-407). Importantly, recommendations from the Society for Immunotherapy of Cancer (SITC) emphasize that for PD-L1 assessment, *"the 22C3, 28–8, and SP263 assays are interchangeable. The SP142 assay is not interchangeable and does not perform equivalently to the other assays listed"* (8).

B.1.3.4 Clinical presentation, diagnosis and staging

Early-stage NSCLC is largely asymptomatic, and the UK Government recommends targeted lung cancer screening for people aged 55 to 74 years who are at high risk of lung cancer (18). In 2022, 34% of people diagnosed with lung cancer in England were diagnosed at an early stage (19), meaning that most patients have advanced disease at diagnosis. Patients with advanced disease commonly present with cough; other symptoms include dyspnoea, haemoptysis and pain (20). Patients with metastatic disease may also have more systemic symptoms such as headache, hepatomegaly, mental status changes, weakness and seizures (20).

NSCLC is diagnosed using a combination of histological analysis, molecular testing for genetic mutations and IHC assays for PD-L1 expression. Despite the importance of genetic testing in determining suitable treatment options, a recent study showed that there is variation in mutation testing practices across the UK, which may impact treatment decisions and contribute to health outcome inequality (21).

NSCLC is staged according to the TNM classification system, which evaluates the size and characteristics of a tumour (T = tumour), the extent to which the cancer has spread to the local lymph node system (N = node) and the presence of metastases to distant tissues or organs (M = metastases). Once the TNM components have been assessed, an overall stage is assigned, ranging from 0 (early disease) to IV (metastatic disease) (22). Locally advanced disease is classified as Stage IIIB/IIIC.

The most common sites of metastases in NSCLC are the bone (34.3%), lung (32.1%) and brain (28.4%) (23).

B.1.3.5 Epidemiology and risk factors

Based on an incidence rate of 0.065% (calculated using reported cases in England and Wales for 2022 according to National Lung Cancer Audit data (19) and population data from the Office of National Statistics), it is estimated that there were 37,259 cases of lung cancer in England and Wales in 2023. Of these, 34,129 were NSCLC (23,891 were non-squamous disease and 10,239 were squamous disease). It is estimated that there will be approximately 4,844 patients with NSCLC in England who will receive systemic anticancer therapy and would be eligible for treatment with cemiplimab + chemotherapy within its licensed indication in 2025, rising to 5,143 in 2029.

The incidence of lung cancer is related to age, rising steeply from age 45 to 59 years and peaking at 75 to 79 years in women and 85 to 89 years in men (24).

Smoking is the most significant risk factor for development of NSCLC. Other risk factors include exposure to radon (including from domestic residential sources and passive emission from the soil), exposure to asbestos, air pollution and a family history of lung cancer.

B.1.3.6 Burden of NSCLC

Patients with advanced NSCLC bear a substantial mortality, clinical, humanistic, and economic burden. The high symptom burden negatively affects health-related quality of life (HRQoL) and the functional status of patients and caregivers (25, 26). Side effects from chemotherapy also place a considerable burden on patients, caregivers and the NHS (see Section B.1.3.8 for further details).

Data from one of the largest comorbidity studies carried out in England show that 67% of patients diagnosed with lung cancer have at least one comorbidity, including chronic obstructive pulmonary disease, hypertension and renal disease (27). Management of these comorbidities places an economic burden on healthcare systems; renal disease is one of the most costly conditions to manage among cancer patients, contributing to 17% of the costs of the cancer (27). More than 15% of patients with lung cancer present with renal dysfunction (eGFR <60) (28). This is to be expected, given that the incidence of lung cancer increases with age and renal function declines with age.

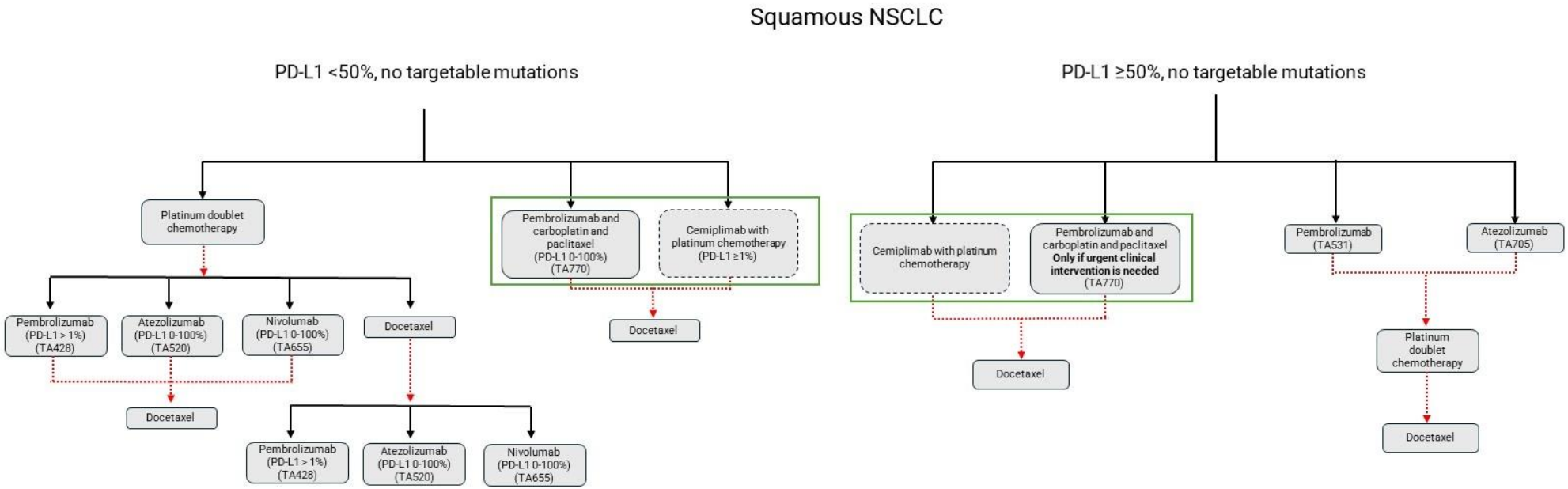
Patients with comorbidities may have a higher risk of experiencing adverse events from cancer treatment (27). In non-squamous disease, pemetrexed is used as part of the chemotherapy backbone for pembrolizumab + chemotherapy regimens, and is widely used as maintenance treatment after initial IO + chemotherapy. However, pemetrexed is associated with renal toxicity and is not recommended for use in patients with creatinine clearance <45 mL/min (an estimated 8% of the total cancer population (29)) (30). Renal impairment caused by pemetrexed can be sustained after treatment stops, and may jeopardise subsequent lines of treatment (31).

The prognosis of patients with advanced lung cancer is poor. Between 2013-2017 (i.e. before the introduction of IO), patients in England diagnosed with Stage IV lung cancer had a five-year net survival rate of just 2.9% compared with 12.6% for Stage III, 34.1% for Stage II and 56.6% for Stage I (32). UK patients have poorer survival relative to those in other European countries (33). Although the introduction of IO has improved survival for patients with advanced NSCLC, the burden of disease remains significant and there is a need for additional treatment options.

B.1.3.7 Clinical pathway of care

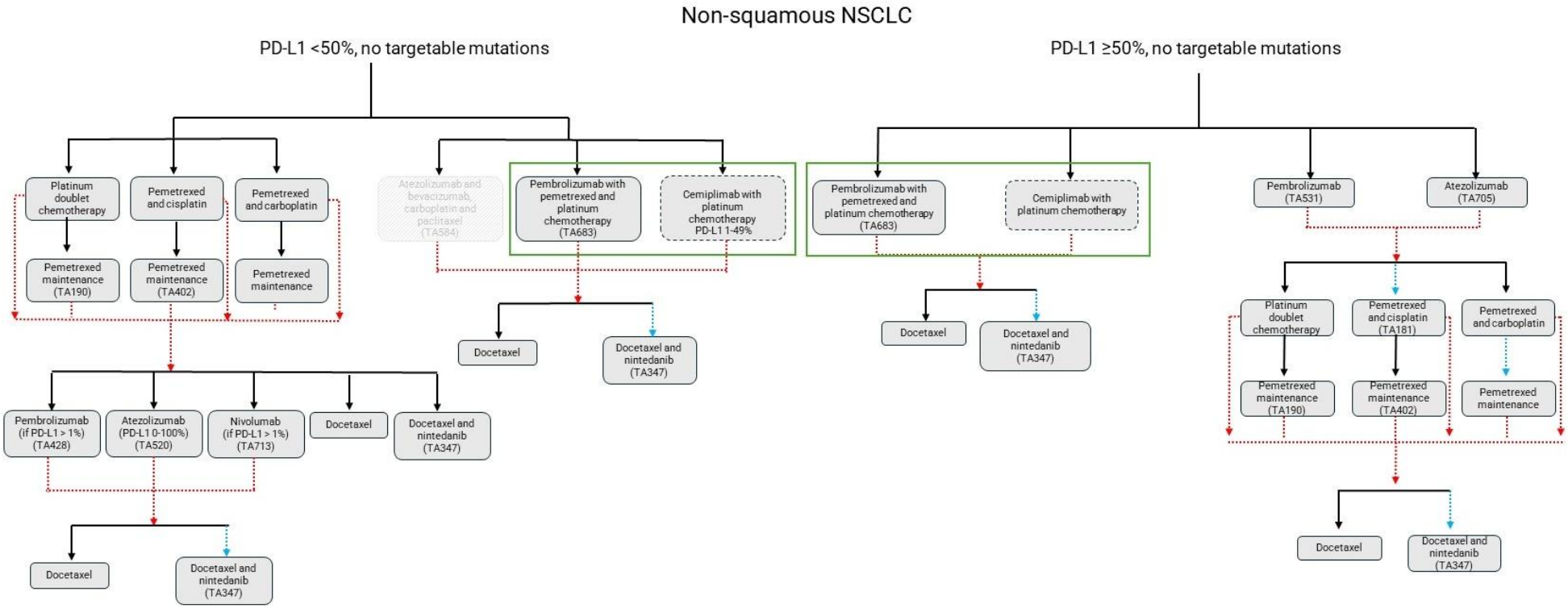
For advanced/metastatic NSCLC without targetable driver mutations, systemic therapy is the mainstay of treatment, with IO (± platinum-based chemotherapy) as routine for all patients unless contra-indicated. The current NICE NSCLC guideline (NG122) gives recommendations for first-line treatment with decision nodes based on histology and PD-L1 levels (34). These recommendations are shown in Figure 1 and Figure 2, which also show the anticipated position of cemiplimab + chemotherapy in the treatment pathway.

Figure 1 Treatment pathway: squamous NSCLC



Red arrows denote disease progression; Green boxes denote relevant comparison for the decision problem
TA428: Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (35); TA520: Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (36); TA655: Nivolumab for advances squamous non-small-cell lung cancer after chemotherapy (37); TA770: Pembrolizumab with carboplatin and paclitaxel for untreated squamous non-small-cell lung cancer (38); TA531: Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (39); TA705 : Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer (40). Note: NHS England commissioning policy (1) includes use of pembrolizumab + chemotherapy in the treatment of locally advanced NSCLC, in addition to its licensed use in metastatic disease per TA770.
Source : Adapted from NICE NG122 (34)

Figure 2 Treatment pathway: non-squamous NSCLC



Red arrows denote disease progression; Blue arrows denote NHS England policy; Green box denotes comparison relevant to the decision problem

TA190: Pemetrexed for the maintenance of non-small-cell lung cancer (41); TA402: Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (42); TA584: Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (43); TA683: Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (44); TA428: Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (35); TA520: Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (36); TA713: Nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy (45); TA347: Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (46); TA531: Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (39); TA705 : Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer (40). Note: NHS England commissioning policy (1) includes use of pembrolizumab + chemotherapy in the treatment of locally advanced NSCLC, in addition to its licensed use in metastatic disease per TA770

Source : Adapted from NICE NG122 (34)

As shown in Figure 1 and Figure 2, IO + chemotherapy is the only IO option in patients with PD-L1 levels 1-49%, and is therefore standard of care in this population. For patients with PD-L1 ≥50%, both IO monotherapy and IO + chemotherapy are available; and clinicians face a complex decision regarding which might be the most suitable option. Feedback from UK clinical expert lung oncologists has revealed that they would consider using an IO + chemotherapy combination in patients with PD-L1 levels ≥50% depending on a range of factors, including disease burden, symptoms, smoking status/history and age (47).

Clinicians also highlighted practical considerations that influence the choice between monotherapy and combination therapy, such as delays in the diagnostic pathway and differences between regions/centres in chemotherapy unit capacity and preference for Q6W vs Q3W dosing (47).

Patient preference also plays an important part in treatment decisions. For example, some patients may choose to receive IO alone as they are concerned about the potential side-effects of chemotherapy, such as hair loss. Route of administration and dosing intervals are also a relevant aspect of patient preference.

As shown in Figures 1 and 2, cemiplimab + chemotherapy is positioned as an option for patients with PD-L1 expression ≥1% who would typically receive pembrolizumab + chemotherapy in both squamous and non-squamous locally advanced/metastatic NSCLC. As discussed in Section B.1.1, Regeneron consider pembrolizumab + chemotherapy, with >80% of current UK market share in the any histology, PD-L1 ≥1% population (2), to be the relevant comparator for this appraisal.

- Patients offered IO + chemotherapy comprise a patient group who are clinically distinct from those who would typically be offered chemotherapy alone because they are not considered suitable for IO, or from those who would typically be offered an IO monotherapy instead of in combination with chemotherapy

- Atezolizumab combination therapy is available for use only in people with non-squamous disease and PD-L1 1-49%, and is not commonly used in UK

clinical practice (having approximately 8% of market share in this subpopulation (2)).

Of note, the ESMO guidelines for metastatic NSCLC include cemiplimab + chemotherapy as an alternative to other IO + chemotherapy combinations (48). In addition, cemiplimab + chemotherapy is the only IO + chemotherapy combination other than pembrolizumab + chemotherapy that has a 'preferred' NCCN guidelines recommendation for the treatment of patients with advanced/metastatic NSCLC (49). NCCN has assigned both options with a score of 4 out of 5 ('very effective') for efficacy across histology and PD-L1 subgroups in its Evidence Blocks™ assessment. This is based on an assessment taking into account both published trial evidence and real-world clinical experience of the panel members in more diverse real-world settings. Cemiplimab + chemotherapy also has a more favourable NCCN Evidence Blocks safety score (3, mildly toxic) than pembrolizumab + chemotherapy (2, moderately toxic) in patients with squamous histology and PD-L1 1-49% (49).

B.1.3.8 Unmet need

Cemiplimab + chemotherapy gives clinicians greater flexibility to tailor chemotherapy treatment to individual patient characteristics, needs, and preferences

In England, pembrolizumab + chemotherapy is the current standard of care IO + chemotherapy option across histologies and PD-L1 levels. Based on the registrational KEYNOTE studies, the Blueteq protocol (i.e. NHS England commissioning policy) for pembrolizumab specifies that squamous patients should be "fit for AUC6" carboplatin and only lists pemetrexed-containing regimens for people with non-squamous disease (1). However, pemetrexed is associated with toxicities such as pneumonitis, rash, colitis, hypo- and hyperthyroidism, and nephritis, and the use of pemetrexed in patients with creatinine clearance <45 ml/min is not recommended (30). In KEYNOTE-189, 23% of patients who received pembrolizumab + chemotherapy discontinued pemetrexed because of adverse events (AEs) (16).

UK clinical expert lung oncologists consulted during development of this submission indicated that carboplatin AUC6 dosing is associated with additional toxicity (thrombocytopenia, fatigue, renal dysfunction) and is less well tolerated than AUC5

dosing. The experts stated that a AUC5 dosing option would be helpful and valuable (47). According to a 2020 review by Fowler et al, *"Clinical guidelines in the United Kingdom are not accommodating to the cumulative impact of treatment recommendations on those with multiple morbidities, and do not facilitate a comparison of potential risks of benefits"* (27).

Side effects from chemotherapy represent a high burden to NSCLC patients; in some cases the treatment burden is higher than the symptom burden of the cancer (50). Patients state that they would like treatments with minimal side effects so that they can carry on with their regular activities while receiving treatment (50).

Side effects of chemotherapy also place a burden on caregivers. Caregivers report that seeing a patient experience side effects is particularly challenging and that they often feel conflicted between wanting the patient to receive treatment but not wanting them to suffer side effects (50).

Managing the side effects of chemotherapy is also associated with substantial resource use and costs to the NHS.

Several studies in non-lung cancers have described need for flexibility in tailoring chemotherapy regimens according to patients' characteristics and their ability to tolerate existing options (51-53).

In expectation that the Blueteq protocol (i.e. NHS commissioning policy) for cemiplimab + chemotherapy would be aligned with the key registrational RCT informing this appraisal (i.e. EMPOWER-Lung 3), routine availability of cemiplimab + chemotherapy would give clinicians greater flexibility to tailor chemotherapy to individual patient characteristics, needs, and preferences. In EMPOWER-Lung 3, [redacted] patients ([redacted]%) with non-squamous histology who were randomised to cemiplimab + chemotherapy received a pemetrexed-free regimen (cemiplimab + paclitaxel + carboplatin). EMPOWER-Lung 3 also allowed use of AUC5 carboplatin. A total of [redacted] patients ([redacted]%) with squamous histology in the cemiplimab + chemotherapy group received carboplatin; [redacted] ([redacted]%) were selected to receive AUC5 at baseline based in information provided on the study case report forms. See Section B.2.4.4 for further details.

The UK clinical expert lung oncologists agreed that this additional upfront flexibility in the chemotherapy dose/agent that could be used in combination with an IO would be a useful and helpful option (47). Such flexibility would be in line with the NHS standard contract for cancer chemotherapy, which states that *"The service should be actively working towards personalising treatment, with service flexibility to match the individual's needs and those of their carers"* (54).

Existing IO + chemotherapy regimens are costly

Pembrolizumab + chemotherapy currently has market dominance, with >80% of the UK market share in the any histology, PD-L1 ≥1% population (2). There is a need for alternatives that will drive cost savings in the NHS by providing competition and potentially avoiding AEs/complications by allowing clinicians to better tailor treatment according to individual patient needs. There is also the potential to improve NHS supply chain resilience by having an alternative to the current market-dominant option.

A systematic review of PD-1 inhibitors in advanced oesophageal squamous cell cancer found that despite the improved survival rates seen with IO, there is still a considerable economic burden on patients and healthcare systems (55). There is therefore a need for an alternative cost-saving IO that would reduce this burden. Increased competition resulting from the launch of a therapy in new indications may drive down prices and healthcare system costs (56). According to Goldstein et al (2024), interchangeability between members of a class of anti-cancer drugs could allow for cost savings and improved access to treatment (57).

There is no other licensed IO + chemotherapy option for patients with locally advanced disease

The registrational studies for pembrolizumab + chemotherapy did not include patients with locally advanced disease, and use of pembrolizumab + chemotherapy in this patient group per NHS England commissioning policy (i.e. the Blueteq protocol) is therefore off-label.

Based on EMPOWER-Lung 3, which demonstrated effectiveness of cemiplimab + chemotherapy in a diverse cohort including patients with both locally advanced (not eligible for chemoradiation) and metastatic disease, the approved MHRA label indication statement for cemiplimab includes patients with locally advanced disease who are not eligible for definitive chemoradiation.

B.1.4 Equality considerations

Regeneron does not anticipate that the use of cemiplimab in combination with chemotherapy will raise any equality issues.

B.2 Clinical effectiveness

B.2.1 List of relevant clinical effectiveness evidence

There are no RCTs that compare cemiplimab + chemotherapy with the only relevant comparator for this appraisal (i.e. pembrolizumab + chemotherapy; Table 1), or with any other IO treatment. Relevant evidence for the clinical effectiveness of cemiplimab + chemotherapy comes from the pivotal EMPOWER-Lung 3 RCT (Table 3), which compared cemiplimab + chemotherapy with placebo + chemotherapy as first-line treatment for patients with advanced NSCLC (unresectable locally advanced disease not suitable for definitive chemoradiation or metastatic disease).

EMPOWER-Lung 3 was composed of two independent parts:

- Part 1 evaluated cemiplimab + abbreviated chemotherapy + ipilimumab or cemiplimab + chemotherapy *versus* platinum doublet chemotherapy in patients with PD-L1 <50%
- Part 2 evaluated cemiplimab + platinum-based doublet chemotherapy *versus* placebo + platinum-based doublet chemotherapy in patients with any PD-L1 expression level

Parts 1 and 2 are considered distinct studies, with separate randomisation schemes, inclusion criteria and visit/event schedules. Patients enrolled in Part 1 do not contribute to the analyses in Part 2 and vice versa. This submission focuses on Part 2; Part 1 is not considered relevant to the decision problem owing to its patient population and is not discussed further.

Although EMPOWER-Lung 3 enrolled patients regardless of PD-L1 status, the EMA and MHRA subsequently licensed cemiplimab + chemotherapy for use in patients with PD-L1 ≥1% (58). This submission therefore focuses on those patients in EMPOWER-Lung 3 with PD-L1 ≥1% (referred to as the ‘MHRA label population’). Efficacy results are presented for this population in Section B.2.6 with results for the ITT population (i.e. any PD-L1) summarised in Appendix M. Safety results are presented for the safety analysis set (i.e. all patients who received at least one dose

of study medication) to maximise the sample size, as safety outcomes are not anticipated to be affected by PD-L1 expression.

Table 3 Clinical effectiveness evidence

Study	EMPOWER-Lung 3 (NCT03409614); part 2
Study design	Randomised, double-blind, placebo-controlled, Phase 3
Population	Patients with untreated advanced squamous or non-squamous NSCLC with no *EGFR*, *ALK* or *ROS1* aberrations, irrespective of PD-L1 expression
Intervention(s)	Cemiplimab 350 mg IV Q3W plus 4 cycles of chemotherapy[a]
Comparator(s)	Placebo IV Q3W plus 4 cycles of chemotherapy[a]
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem[b]	**Progression-free survival**, response rates, **overall survival**, **adverse effects of treatment**, health-related quality of life
All other reported outcomes	Duration of response

[a]Full details of permitted chemotherapy regimens are given in Table 5.
Outcomes in bold are included in the economic model
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1; Q3W, every 3 weeks; ROS1, proto-oncogene tyrosine-protein kinase ROS

Table 4 lists the available full publications for EMPOWER-Lung 3 (Part 2).

Table 4 Full publications based on EMPOWER-Lung 3 (Part 2)

Author	Year	Description
Gogishvili, et al (59)	2022	1-year follow up data (primary OS analysis)
Makharadze, et al (60)	2023	2-year follow up data (ITT population)
Makharadze, et al (61)	2023	2-year follow up data (ITT population): erratum
Makharadze, et al (62)	2023	HRQoL data (ITT population)
Baramidze, et al (63)	2024[a]	2-year follow-up data (MHRA label population)

[a]Not captured in SLR owing to publication after the search cut-off. However, it is included in the submission as the data are highly relevant to the decision problem
HRQoL, health-related quality of life; ITT, intention-to-treat; MHRA, Medicines and Healthcare products Regulatory Agency; OS, overall survival

In addition, data from the study have been presented at a number of international congresses (64-74). This includes HRQoL data in the PD-L1 ≥1%, any histology (MHRA label) population (68) and subgroup analyses in patients with squamous disease (72) and liver metastases (64, 65).

B.2.2 Identification and selection of relevant studies

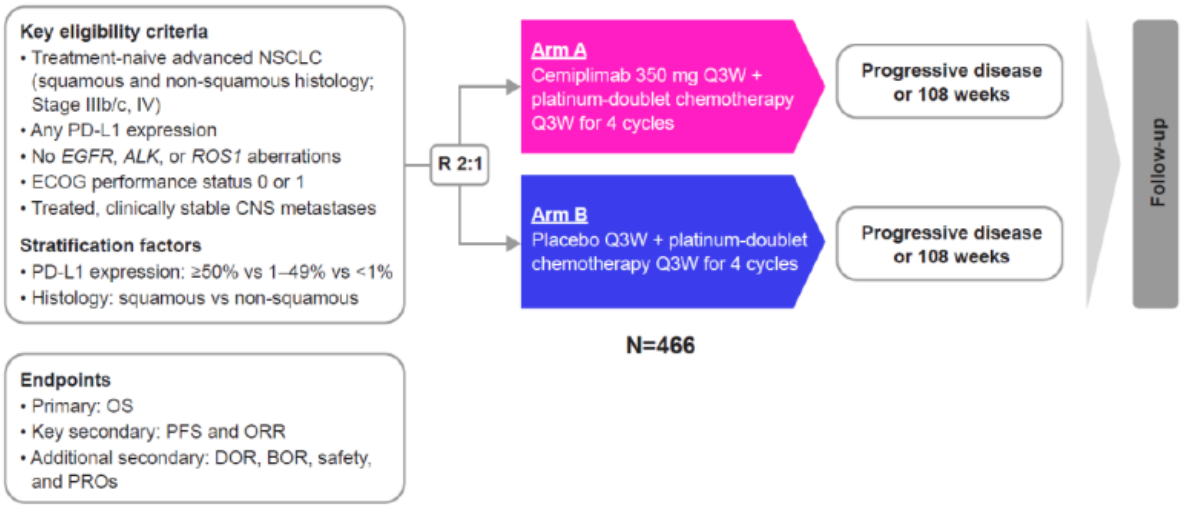
A systematic literature review (SLR) was carried out to identify clinical evidence relevant to the decision problem. Full details can be found in Appendix D.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 EMPOWER-Lung 3: methods

Figure 3 shows the study design for Part 2 of EMPOWER-Lung 3. The study had broad inclusion criteria, enrolling patients with advanced NSCLC of any PD-L1 expression level. Key eligibility criteria included previously untreated metastatic NSCLC, locally advanced NSCLC, not candidates for surgical resection or definitive chemoradiation, any PD-L1 expression level, and ECOG PS 0 or 1. The study also allowed enrolment of patients with treated, clinically stable brain metastases, squamous and non-squamous histologies, and controlled hepatitis B, hepatitis C or HIV. Further details are given in Table 5 and the study protocol (59).

Figure 3 EMPOWER Lung-3 study design



ALK, anaplastic lymphoma kinase; BOR, best overall response; CNS, central nervous system; DOR, duration of response; EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PROs, patient-reported outcomes; Q3W, every 3 weeks; ROS1, ROS proto-oncogene 1
Source: Makharadze et al, 2023 (60)

Eligible patients were randomised 2:1 to either cemiplimab 350 mg Q3W combined with 4 cycles of platinum-based doublet chemotherapy or placebo Q3W combined with 4 cycles of platinum-based doublet chemotherapy. Randomisation was stratified by histology (squamous vs non-squamous) and PD-L1 expression levels (<1% vs 1%-49% vs ≥50%). The squamous patient population was capped at 50%. At least 30% but ≤40% patients enrolled were to have PD-L1 expression levels ≥50%; enrolment of patients with PD-L1 expression <1% was capped at 30% (consistent with the pivotal trials of pembrolizumab + chemotherapy).

Investigators had a choice of chemotherapy regimens: paclitaxel plus carboplatin, paclitaxel plus cisplatin, pemetrexed plus carboplatin or pemetrexed plus cisplatin. Maintenance pemetrexed was mandatory for patients with non-squamous disease assigned to a pemetrexed-containing regimen.

Patients received treatment for up to 108 weeks, or until disease progression or unacceptable toxicity.

Table 5 summarises the methodology of EMPOWER-Lung 3.

Table 5 Summary of trial methodology: EMPOWER-Lung 3 (Part 2)

Trial	**EMPOWER-Lung 3**
Location	74 sites in 10 countries: China, Georgia, Greece, Malaysia, Poland, Romania, Russia, Thailand, Turkey, Ukraine
Trial design	Phase 3, randomized, double-blind study to compare the efficacy and safety of cemiplimab/chemo versus placebo/chemo in patients with locally advanced or metastatic squamous or non-squamous NSCLC irrespective of PD-L1 levels. Patients were treated for 108 weeks or until disease progression, whichever occurred first.
Eligibility criteria for participants	Key inclusion criteria:[a] • Age ≥18 years (≥20 years for Japanese patients) • Availability of an archival or on-study obtained formalin-fixed, paraffin-embedded tumour tissue sample • ≥1 radiographically measurable lesion per RECIST 1.1 • Histologically or cytologically confirmed squamous or non-squamous IIIB/C (if deemed not candidates for definitive chemoradiation) or stage IV NSCLC • ECOG PS ≤1 • Anticipated life expectancy ≥3 months • Adequate organ and bone marrow function Key exclusion criteria:[a] • Active or untreated brain metastases or spinal cord compression (patients with adequately treated and clinically stable brain metastases were eligible) • Tumours positive for *EGFR* mutations, *ALK* translocations or *ROS1* fusions • Prior anti-PD-1/PD-L1 therapy • Treatment-related immune-mediated AEs from immune-modulatory agents • History of interstitial lung disease, including active, non-infective pneumonitis, or with active, known or suspected autoimmune disease that required systemic treatment in the past 2 years

Settings and locations where the data were collected	Trial drugs were administered in the outpatient infusion setting at the study sites. Radiographic tumour assessments were carried out at the study sites every 9 weeks (beginning at Week 9) during Year 1 and every 12 weeks (beginning at Week 55) during Year 2; these were reviewed by a blinded IRC to determine tumour response. Survival data were collected by phone or at an office visit every 3 months until death, loss to follow-up or withdrawal of study consent.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	Patients were randomised 2:1 to receive either: • Cemiplimab 350 mg IV Q3W in combination with four cycles of chemotherapy (n = 312) or • Placebo IV Q3W in combination with four cycles of chemotherapy (n = 154) Investigators could choose from the following chemotherapy options: • Paclitaxel 200 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/min[b] IV on Day 1 every 21 days for 4 cycles • Paclitaxel 200 mg/m^2 IV plus cisplatin 75 mg/m^2 IV Day 1 every 21 days for 4 cycles • Pemetrexed 500 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/min[b] IV Day 1 every 21 days for 4 cycles • Pemetrexed 500 mg/m^2 IV plus cisplatin 75 mg/m^2 IV Day 1 every 21 days for 4 cycles Patients were treated for up to 108 weeks or until disease progression or unacceptable toxicity. Pemetrexed maintenance was mandatory for patients with non-squamous disease assigned to a pemetrexed-containing regimen.

Permitted and disallowed concomitant medication	Permitted concomitant medication: • Medication (other than that listed as disallowed) that is considered necessary of the patient's welfare and is not expected to interfere with the action of cemiplimab • Physiologic replacement doses of systemic corticosteroids • Brief course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by contact allergen) • Treatments for bone metastases (e.g. bisphosphonates, denosumab) • Pemetrexed maintenance (only for patients with non-squamous histology allocated to a pemetrexed-containing chemotherapy regimen) Disallowed concomitant medication: • Any investigational drug or treatment for treatment of a tumour, other than the study drugs • Idelalisib, bevacizumab or necitumumab • Systemic corticosteroids (hydrocortisone, prednisone, prednisolone, dexamethasone), except in the case of a life-threatening emergency and/or to treat an immune-related AE
Primary outcomes (including scoring methods and timings of assessments)	Overall survival, defined as the time from randomisation to the date of death due to any cause.
Other outcomes used in the economic model/specified in the scope	• Progression-free survival, defined as the time from randomisation to the date of the first documented tumour progression (as determined by a blinded IRC) or death, whichever occurred earlier • Objective response rate, defined as the proportion of patients with a best overall response of CR or PR, as determined by a blinded IRC • Duration of response, defined as the time from first documented response of CR or PR to the date of first documented PD or death due to any cause, whichever occurred earlier • Best overall response, defined as the best response (as determined by the IRC or investigator per RECIST 1.1) between the date of randomisation and the date of the first objectively documented progression or death due to any cause, whichever occurred earlier • Overall survival rate at 12 months, 18 months and 24 months • Quality of life, as measured by the EORTC QLQ-C30 and EORTC QLQ-LC13 • Adverse effects of treatment
Pre-planned subgroups	Overall survival, progression-free survival and overall response rate by:

	• Age category (≤65 vs. >65 years) • Gender (male, female) • Race (white, non-white) • Histology (squamous, non-squamous) • PD-L1 expression levels (<1% vs. 1% to <50% vs. ≥50%) • ECOG status (0 vs. 1) • Geographic region of enrolling site • Ethnicity

[a]A full list of inclusion and exclusion criteria is available in the supplementary information to Gogishvili et al, 2022 (59). [b]Dose of carboplatin calculated using the Calvert formula.
AE, adverse event; ALK, anaplastic lymphoma kinase; AUC, area under the curve; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer; IRC, independent review committee; IV, intravenous; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; ROS1, ROS proto-oncogene 1
Source: Gogishvili et al, 2022 (59)

B.2.3.2 Baseline demographics and disease characteristics

Table 6 summarises baseline demographics and disease characteristics for the ITT and PD-L1 ≥1% populations. In both populations, baseline and disease characteristics were well balanced between the treatment groups. Most patients were white and male, and more than half were younger than 65 years of age. Most patients were either current or past smokers. Approximately 85% of patients had metastatic disease. The distribution of PD-L1 expression levels was similar between treatment groups.

Table 6 Baseline demographics and disease characteristics

	ITT population			PD-L1 ≥1% (MHRA label) population		
	Cemiplimab + chemo (n = 312)	Placebo + chemo (n = 154)	Total (n = 466)	Cemiplimab + chemo (n = 217)	Placebo + chemo (n = 110)	Total (n = 327)
Age, years						
Median (IQR)	63.0 (57-68)	63.0 (57-68)	63.0 (57-68)	63.0 (56-67)	62.0 (55-66)	62.0 (56-67)
≥65 years, n (%)	128 (41.0)	60 (39.0)	188 (40.3)	88 (40.6)	36 (32.7)	124 (37.9)
Sex, n (%)						
Female	44 (14.1)	31 (20.1)	75 (16.1)	32 (14.7)	22 (20.0)	54 (16.5%)
Male	268 (85.9)	123 (79.9)	391 (83.9)	185 (85.3)	88 (80.0)	273 (83.5)
Geographic region, n (%)						
Europe	270 (86.5)	138 (89.6)	408 (87.6)	187 (86.2)	101 (91.8)	288 (88.1)
Asia	42 (13.5)	16 (10.4)	58 (12.4)	30 (13.8)	9 (8.2)	39 (11.9)
Histology, n (%)						
Non-squamous	179 (57.4)	87 (56.5)	266 (57.1)	122 (56.2)	59 (53.6)	181 (55.4)
Squamous	133 (42.6)	67 (43.5)	200 (42.9)	95 (43.8)	51 (46.4)	146 (44.6)
PD-L1 expression, n (%)						
<1%	95 (30.4)	44 (28.6)	139 (29.8)	N/A	N/A	N/A
1-49%	114 (36.5)	61 (39.6)	175 (37.6)	114 (52.5)	61 (55.5)	175 (53.5)
≥50%	103 (33.0)	49 (31.8)	152 (32.6)	103 (47.5)	49 (44.5)	152 (46.5)
ECOG PS, n (%)						
0	51 (16.3)	18 (11.7)	69 (14.8)	38 (17.5)	15 (13.6)	53 (16.2)

	ITT population			PD-L1 ≥1% (MHRA label) population		
	Cemiplimab + chemo (n = 312)	Placebo + chemo (n = 154)	Total (n = 466)	Cemiplimab + chemo (n = 217)	Placebo + chemo (n = 110)	Total (n = 327)
1	259 (83.0)	134 (87.0)	393 (84.3)	178 (82.0)	94 (85.5)	272 (83.2)
Missing	2 (0.6)	2 (1.3)	4 (0.9)	1 (0.5)	1 (0.9)	2 (0.6)
Brain metastases, n (%)	24 (7.7)	7 (4.5)	31 (6.7)	15 (6.9)	6 (5.5)	21 (6.4)
Cancer stage at screening, n (%)						
Metastatic	267 (85.6)	130 (84.4)	397 (85.2)	187 (86.2)	93 (84.5)	280 (85.6)
Locally advanced	45 (14.4)	24 (15.6)	69 (14.8)	30 (13.8)	17 (15.5)	47 (14.4)
Smoking history, n (%)						
Current smoker	173 (55.4)	75 (48.7)	248 (53.2)	114 (52.5)	53 (48.2)	167 (51.1)
Past smoker	96 (30.8)	55 (35.7)	151 (32.4)	72 (33.2)	40 (36.4)	112 (34.3)
Never smoker	43 (13.8)	24 (15.6)	67 (14.4)	31 (14.3)	17 (15.5)	48 (14.7)

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; ITT, intention to treat; N/A, not applicable; PD-L1 programmed death ligand-1; PS, performance status
Source: Gogishvili et al, 2022 (59); Libtayo EPAR, 2023 (58); Baramidze et al 2024 (63)

B.2.3.3 Methods for eliciting expert opinion

Expert opinion was gathered via several routes. Between January and March 2024, Medical Affairs staff from Regeneron conducted an outreach exercise to: obtain up-to-date knowledge about the IO + chemotherapy landscape in the UK; validate Regeneron's understanding of the lung cancer therapeutic area landscape and treatment pathway; understand how to optimally position cemiplimab + chemotherapy. Nineteen UK-based medical and clinical oncologists were consulted.

The results of the outreach were validated during a medical-led advisory board held in May 2024, which was attended by 10 medical and clinical oncologists who routinely treat patients with locally advanced or metastatic NSCLC and are based at a representative set of centres (both urban and rural) in England. Following the advisory board, the attendees were sent a follow-up questionnaire to elicit further feedback.

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

B.2.4.1 Populations analysed

Efficacy endpoints were assessed in the intention-to-treat (ITT) population, i.e. all patients who were randomised to treatment. The ITT population consisted of 466 patients (312 in the cemiplimab + chemotherapy group and 154 in the placebo + chemotherapy group).

Safety endpoints were assessed in the safety analysis set (SAF), i.e. all patients who received at least one dose of any component of the study treatment. The SAF population consisted of 465 patients (312 in the cemiplimab + chemotherapy group and 153 in the placebo + chemotherapy group).

It is important to note that the study was powered to the ITT population rather than to the MHRA label population (PD-L1 ≥1%). The MHRA label population consisted of 327 patients (217 in the cemiplimab + chemotherapy group and 110 in the placebo + chemotherapy group) and was assessed post-hoc. All analyses of the MHRA label population are therefore exploratory and any reported P-values should therefore be

considered nominal. Note that PD-L1 expression (<1%, 1 to 49%, ≥50%) was a stratification factor in EMPOWER-Lung 3, thereby maintaining randomisation in the PD-L1 ≥1% subset.

B.2.4.2 Statistical analyses

Table 7 summarises the statistical analyses used in EMPOWER-Lung 3. Two prespecified interim OS analyses were planned when approximately 146 deaths (50% of total OS events) and 204 deaths (70% of total OS events) were observed. Timing of the final OS analysis was prespecified to occur when approximately 291 deaths were observed. Data presented in this submission are from the final OS analysis, which had a data cut-off data of 14 June 2022 and represents more than 2 years (28 months) of follow-up. The trial was stopped early on the recommendation of an independent data monitoring committee, owing to superior OS.

Table 7 Summary of statistical analyses

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
EMPOWER Lung-3	The primary hypothesis was that cemiplimab + chemotherapy would prolong OS compared with placebo + chemotherapy	<u>OS and PFS</u> Stratified log-rank test using histology and PD-L1 expression level as stratification factors. HRs and 95% CIs estimated using a stratified Cox regression model using treatment as a covariate and adjusted using the same stratification factors <u>ORR</u> Cochran-Mantel-Haenszel test stratified by histology and PD-L1 expression **Note**: OS, PFS and ORR were tested hierarchically in that order <u>DOR</u> Kaplan-Meier method <u>PROs</u> Overall change from baseline: MMRM TTD: stratified log-rank test. TTD for GHS and QoL functional scales was defined as the time from randomisation to the first observation with a	It was estimated that 450 randomised patients would be needed to give approximately 93% power to detect a statistically significant difference in OS between treatment groups at a two-sided type 1 error level of 0.05	Patients had the right to withdraw from the study at any time for any reason. The investigator or sponsor could also withdraw patients from the study if it was no longer in the patient's interest to continue, or if the patient's continuation in the study put the scientific outcome of the study at risk. Withdrawn patients were not replaced. There were no imputations for missing data. If no imaging/measurement was done at a particular time point, the patient was designated as not evaluable at that time point. **Censoring rules** <u>OS</u> Any patients not known to have died or who were lost to follow-up at the analysis cut-off date were censored at the last date they were known to be alive

		≥10-point decrease and no subsequent observations with a decrease of ≥10-points from baseline while on study. TTD for the symptom scales was defined as the time from randomisation to the first observation with a ≥10-point increase from baseline and no subsequent observations with an increase of <10 points from baseline while on study		PFS Patients were censored according to the following rules: • Patients with no documented tumour progression or death were censored on the date of their last evaluable tumour assessment • Patients with no documented tumour progression or death before initiation of a new anti-tumour therapy were censored on the date of their last evaluable tumour assessment before or on the date of new anti-tumour therapy • Patients who withdrew consent before taking any study drug and therefore had no post-baseline tumour assessment were censored at the sate of randomisation • Patients with no evaluable tumour assessment after randomisation and did not die were censored on the date of randomisation DOR Patients continuing without PD or death due to any cause were censored according to the same rule as for PFS

				<u>OS at 12, 18, 24 months</u> Patients who were not known to have died or who were lost to follow-up were censored at the last date on which they were known to be alive

CI, confidence interval; DOR, duration of response; HR, hazard ratio; MMRM, mixed models for repeated measures; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand-1; PFS, progression-free survival; PRO, patient-reported outcome; TTD, time to definitive clinically meaningful deterioration
Source: Gogishvili et al, 2022 (and supplementary information) (59)

B.2.4.3 Participant flow

Overall, 904 patients entered screening. Of these, 466 were randomised to treatment: 312 to cemiplimab + chemotherapy and 154 to placebo + chemotherapy. This submission presents evidence from a 2-year follow-up of EMPOWER Lung-3 Part 2, with a data cut-off date of 14 June 2022. At data cut-off, the overall mean duration of follow-up for the overall study population was 28.4 months (IQR: 25.9-31.1) in the cemiplimab plus chemotherapy group and 28.7 months (IQR: 26.2-31.0) in the placebo plus chemotherapy group. Twenty patients (6.4%) in the cemiplimab + chemotherapy group and 2 (1.3%) in the placebo plus chemotherapy group were still undergoing treatment. Treatment had been discontinued in 240 patients (76.9%) in the cemiplimab + chemotherapy group and 149 patients (96.8%) on the placebo + chemotherapy group; the primary reason for discontinuation in both groups was disease progression.

A CONSORT diagram for the ITT population showing the flow of participants through the study and reasons for discontinuation is included in Appendix D.

Of the 466 patients randomised to treatment, 327 had PD-L1 ≥1%. Of these, 217 received cemiplimab + chemotherapy and 110 received placebo + chemotherapy. Median follow-up was 28.0 months (IQR: 25.5-30.8).

B.2.4.4 Distribution of chemotherapy regimens

Investigators had flexibility with the dose of carboplatin that could be administered in the study (AUC5 or 6). Figure 4 shows investigators' intended carboplatin dose at baseline according to the case report form; [redacted] of squamous patients were selected to receive carboplatin AUC5 than AUC6. As discussed in Section B.1.3.8, UK clinical expert lung oncologists consider carboplatin AUC6 to be associated with significant toxicity and have indicated that they would find the option to initiate treatment at a lower dose (e.g. AUC5) useful and helpful.

The study also allowed use of a pemetrexed-free regimen (paclitaxel + carboplatin) in patients with non-squamous histology. Approximately [redacted] of patients in the cemiplimab + chemotherapy group received a pemetrexed-free regimen. As discussed in Section B.1.3.8, pemetrexed is associated with significant toxicity and

may not be suitable for all people with non-squamous disease; the option to use a pemetrexed-free regimen (e.g. paclitaxel and carboplatin) alongside an IO in people with non-squamous disease would similarly be useful and helpful.

Figure 4 Distribution of chemotherapy regimens and planned carboplatin doses in the cemiplimab arm of EMPOWER-Lung 3 (Part 2) (ITT population)

Planned carboplatin dose = planned dose as specified on the case report form. AUC, area under the curve; Cb, carboplatin; cemi, cemiplimab; cis, cisplatin, ITT, intention-to-treat; NSCLC, non-small cell lung cancer; pac, pacitaxel ; pem, pemetrexed
Source: Data on file: carboplatin dosing in EMPOWER Lung-3 (75); Data on file: actual treatment – cemiplimab + chemotherapy arm by histology (FAS) (76)

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Table 8 summarises the results of the quality assessment for EMPOWER-Lung 3. The complete assessment is included in Appendix D.

Table 8 Quality assessment results for parallel group RCTs

Trial number (acronym)	EMPOWER-Lung 3
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, apart from one unblinded pharmacists at each investigational site
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No

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).

A full risk of bias assessment for studies used in the NMA is also provided in Appendix D.

B.2.6 Clinical effectiveness results of the relevant studies

Key points

- In the MHRA-label population (PD-L1 ≥1%):
    - Patients treated with cemiplimab + chemotherapy had clinically meaningful improvements in overall survival compared with those who received placebo + chemotherapy (23.5 months vs 12.1 months; HR = 0.51; 95% CI 0.38-0.69; *P*<0.0001)
    - Patients treated with cemiplimab + chemotherapy had clinically meaningful improvements in PFS compared with those who received placebo + chemotherapy (8.3 months vs 5.5 months; HR = 0.48; 95 % CI: 0.37–0.62, P< 0.0001)
    - The ORR was more then doubled in the cemiplimab + chemotherapy group compared with the placebo + chemotherapy group (47.9% vs 22.7%)
    - The duration of response was notably longer with cemiplimab + chemotherapy than with placebo + chemotherapy (17.5 months vs 6.5 months)

This submission presents evidence from the pre-specified final analysis of EMPOWER Lung-3 (data cut-off date 14 June 2022), which represents approximately 2 years of follow-up (60). At data cut-off, the overall mean duration of follow-up for the overall study population was 28.4 months (IQR: 25.9-31.1) in the

cemiplimab + chemotherapy group and 28.7 months (IQR: 26.2-31.0) in the placebo + chemotherapy group.

The PD-L1 ≥1% population is the focus of this submission, as this reflects the MHRA label. Results for the overall (ITT) population are summarised in Appendix M.

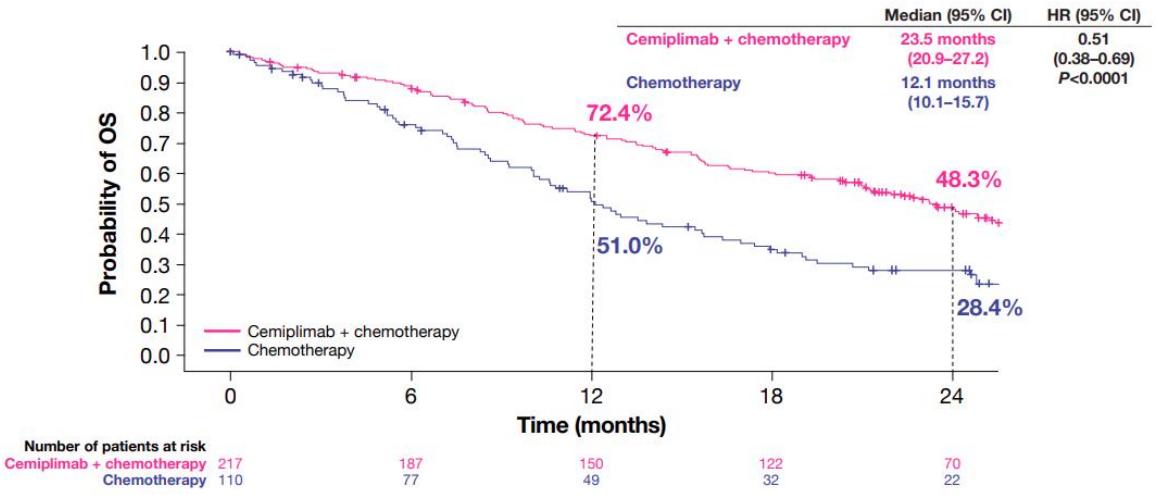
B.2.6.1 PD-L1 ≥1% population

At data cut-off (14 June 2022), the median duration of follow-up in the PD-L1 ≥1% population was 28 months (63).

B.2.6.1.1 Overall survival (primary endpoint)

Patients treated with cemiplimab + chemotherapy showed a clinically meaningful overall survival benefit compared with those who received placebo + chemotherapy. Median OS was 23.5 months in the cemiplimab + chemotherapy group vs 12.1 months in the placebo + chemotherapy group (HR = 0.51; 95% CI 0.38-0.69; *P*<0.0001) (Figure 5).

Figure 5 Overall survival: EMPOWER Lung-3 MHRA label population (PD-L1 ≥1%)



Data cut off: 14 June 2022. CI, confidence interval; HR, hazard ratio; OS, overall survival

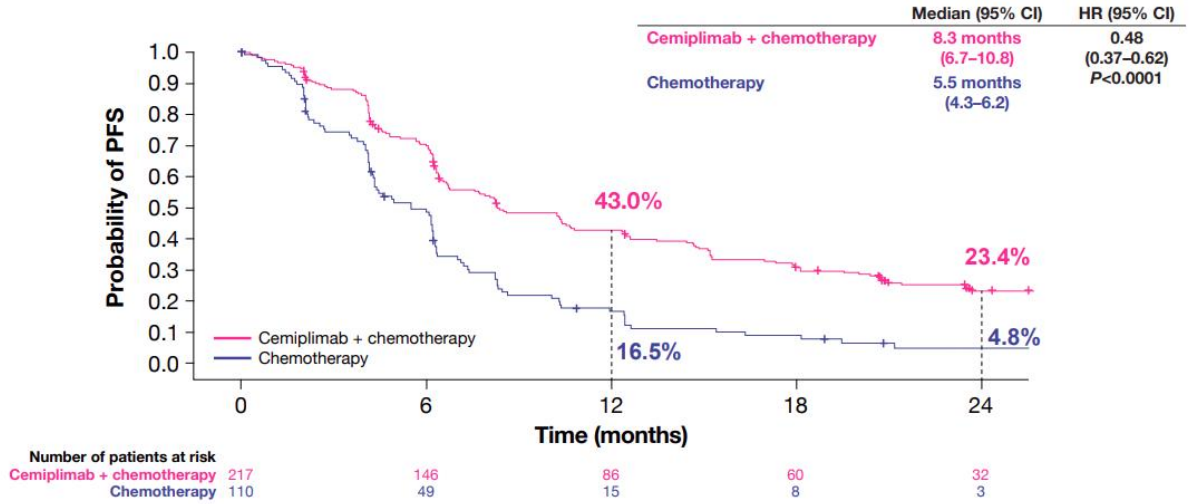
Source: Baramidze et al, 2024 (63)

The estimated probability of survival at 24 months was 48.3% (95% CI: 41.0, 55.1) in the cemiplimab + chemotherapy group, compared with 28.4% (95% CI: 19.8, 37.7) in the placebo + chemotherapy group (63).

B.2.6.1.2 Progression-free survival (secondary endpoint)

Patients treated with cemiplimab + chemotherapy showed a clinically meaningful progression-free survival benefit compared with those who received placebo + chemotherapy. Median PFS was 8.3 months in the cemiplimab + chemotherapy group vs 5.5 months in the placebo + chemotherapy group (HR = 0.48; 95% CI 0.37-0.62; *P*<0.0001) (Figure 6).

Figure 6 Progression-free survival: EMPOWER Lung-3 MHRA label population (PD-L1 ≥1%)



Data cut off: 14 June 2022. CI, confidence interval; HR, hazard ratio; OS, overall survival
Source: Baramidze et al, 2024 (63)

The estimated probability of a patient being progression-free at 24 months was 23.4% (95% CI: 17.7, 29.6) in the cemiplimab + chemotherapy group, compared with 4.8% (95% CI: 1.5, 11.1) in the placebo + chemotherapy group.

B.2.6.1.3 Objective response rates and best overall response (secondary endpoints)

The ORR was more than doubled in the cemiplimab + chemotherapy group compared with the placebo + chemotherapy group (Table 9).

Table 9 Objective response rate: EMPOWER Lung-3 MHRA label population (PD-L1 ≥1%)

	Cemiplimab + chemo (n = 217)	Placebo + chemo (n = 110)
ORR, % (95% CI)	47.9 (41,1, 54.8)	22.7 (15.3, 31.7)
OR (95% CI)	3.12 (1.86, 5.52)	
P value	<0.0001	

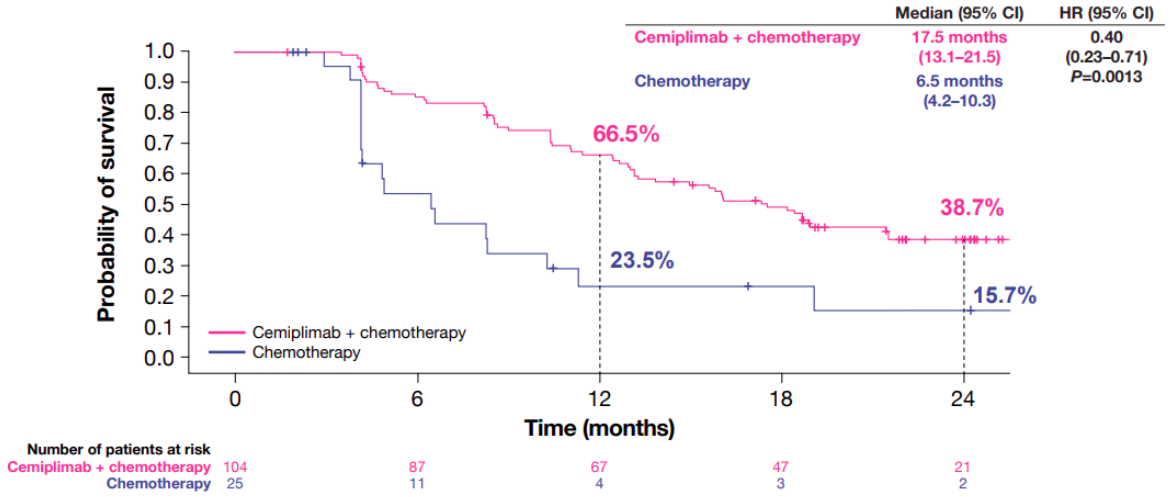
CI, confidence interval; OR, odds ratio; ORR, objective response rate
Source: Baramidze et al, 2024 (63)

In the cemiplimab + chemotherapy group, 11 patients (5.1%) achieved a CR and 93 (42.9%) achieved a PR. No patients in the placebo + chemotherapy group achieved a CR; 25 (22.7%) achieved a PR.

B.2.6.1.4 Duration of response (secondary endpoint)

The median duration of response was 17.5 months in the cemiplimab + chemotherapy group and 6.5 months in the placebo + chemotherapy group (HR = 0.40; 95% CI 0.23, 0.71; *P* = 0.0013) (Figure 7).

Figure 7 Duration of response: EMPOWER Lung-3 MHRA label population (PD-L1 ≥1%)



Data cut off: 14 June 2022. CI, confidence interval; HR, hazard ratio; OS, overall survival
Source: Baramidze et al, 2024 (63)

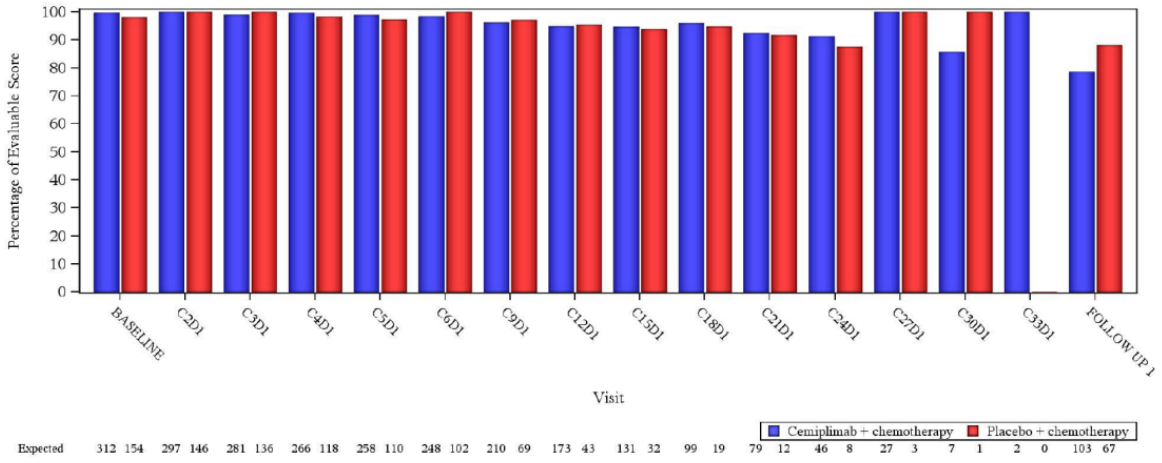
B.2.6.1.5 Health-related quality of life (EORTC QLQ-C30/QLQ-LC13; secondary endpoints)

HRQoL was assessed using the EORTC QLQ-C30 questionnaire and its Lung Cancer Module (QLQ-LC-13). The EORTC QLQ-C30 consists of five multi-item

functioning subscales, three multi-item symptom scales, a global health status (GHS)/QoL subscale, and six single-item symptom scales assessing other disease- and treatment- related symptoms (77). The EORTC QLQ-LC-13 lung cancer-specific module consists of multi-item and single-item measures of lung cancer–associated symptoms (i.e. coughing, hemoptysis, dyspnea, site-specific pain) and side-effects from therapy (i.e. hair loss, neuropathy, sore mouth, dysphagia) (78). Responses are normalised to a 0-100 scale. For functioning and GHS/QoL scales, higher scores correspond to a better level of functioning and QoL; therefore a negative change from baseline corresponds to deterioration, and a positive change corresponds to improvement. For symptom scales, a higher score corresponds to a higher level of symptom severity; therefore, a negative change from baseline in symptom scales corresponds to an improvement and a positive change corresponds to deterioration.

There were no updates to PRO data after the 1-year follow-up; therefore the data presented are from the 14 June 2021 data cut-off. Completion rates for the questionnaires were high: in the ITT population, for every cycle from baseline to cycle 21, ≥92% of patients in the cemiplimab plus chemotherapy group and ≥91% in the placebo plus chemotherapy group completed at least one question on the EORTC QLQ-C30 (Figure 8); similarly, ≥92% and ≥91% of patients, respectively, completed at least one question on the EORTC QLQ-LC13 (62).

Figure 8 PRO completion rate on the EORTC QLQ-C30 Global Health Status/Quality of Life (FAS)



Data cut-off: 14 June 2021
EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; FAS, full analysis set; PRO, patient-reported outcome
Source: Libtayo EPAR (58)

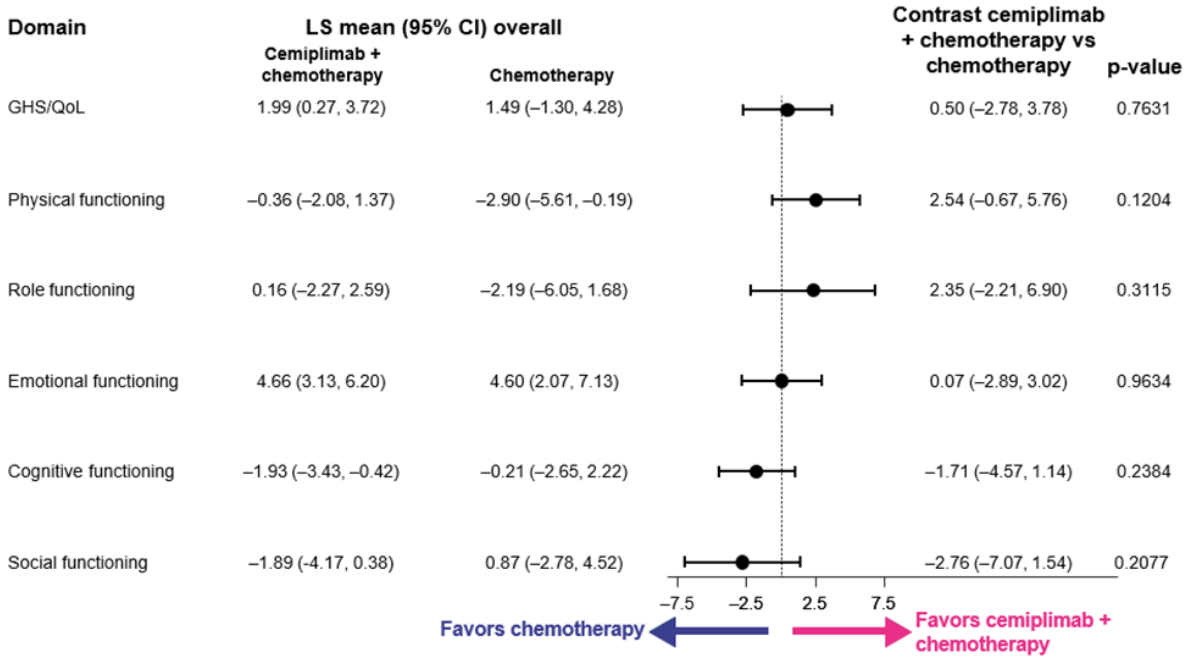
Results for the MHRA label population are presented in this section. Results for the ITT population (which were used for utility mapping with the assumption that health state utility values are not affected by PD-L1 expression) are shown in Appendix M. Results for the MHRA label population were consistent with those for the ITT population.

Baseline mean scores for global health status/quality of life, functioning and symptoms were broadly similar between the treatment groups (see Appendix N) (68).

Figure 9 shows the results of the MMRM analysis of the change from baseline in PROs. There was an overall improvement from baseline favouring cemiplimab + chemotherapy in pain symptoms (Figure 9b). There were no other notable differences between treatment groups.

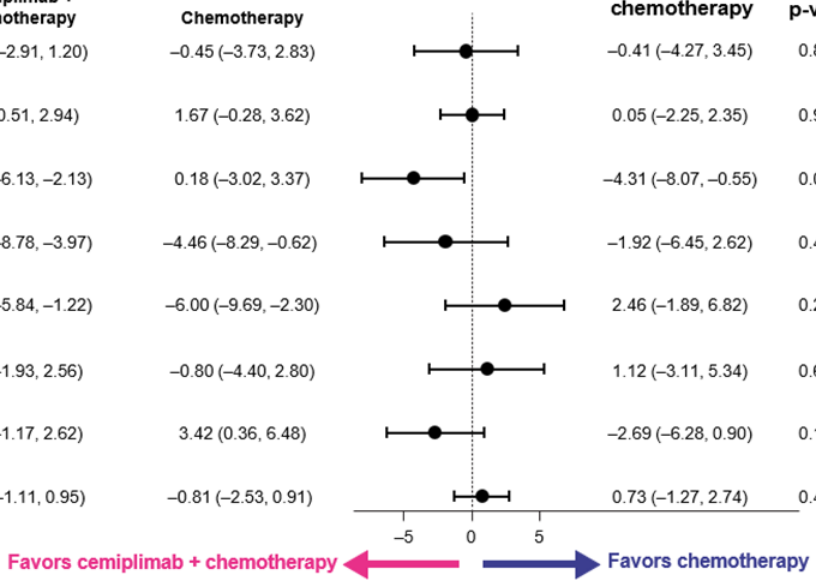
Figure 9 Forest plot for change from baseline in PROs: EMPOWER Lung-3 MHRA label population (PD-L1 ≥1%)

(a) GHS/QoL and EORTC QLQ-C30 functioning



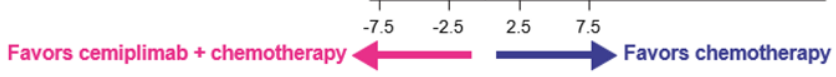
(b) EORTC QLQ-C30 symptoms

Domain	LS mean (95% CI) overall: Cemiplimab + chemotherapy	LS mean (95% CI) overall: Chemotherapy	Contrast cemiplimab + chemotherapy vs chemotherapy	p-value
Fatigue	–0.86 (–2.91, 1.20)	–0.45 (–3.73, 2.83)	–0.41 (–4.27, 3.45)	0.8363
Nausea/vomiting	1.72 (0.51, 2.94)	1.67 (–0.28, 3.62)	0.05 (–2.25, 2.35)	0.9637
Pain	–4.13 (–6.13, –2.13)	0.18 (–3.02, 3.37)	–4.31 (–8.07, –0.55)	0.0248
Dyspnea	–6.38 (–8.78, –3.97)	–4.46 (–8.29, –0.62)	–1.92 (–6.45, 2.62)	0.4058
Insomnia	–3.53 (–5.84, –1.22)	–6.00 (–9.69, –2.30)	2.46 (–1.89, 6.82)	0.2664
Appetite loss	0.31 (–1.93, 2.56)	–0.80 (–4.40, 2.80)	1.12 (–3.11, 5.34)	0.6038
Constipation	0.72 (–1.17, 2.62)	3.42 (0.36, 6.48)	–2.69 (–6.28, 0.90)	0.1410
Diarrhea	–0.08 (–1.11, 0.95)	–0.81 (–2.53, 0.91)	0.73 (–1.27, 2.74)	0.4711



(c) EORTC QLQ-LC13 symptoms

Domain	LS mean (95% CI) overall: Cemiplimab + chemotherapy	LS mean (95% CI) overall: Chemotherapy	Contrast cemiplimab + chemotherapy vs chemotherapy	p-value
LC - Dyspnea	–3.77 (–5.87, –1.67)	–2.76 (–6.01, 0.49)	–1.01 (–4.88, 2.85)	0.6071
LC - Coughing	–12.40 (–14.69, –10.11)	–12.04 (–15.71, –8.37)	–0.36 (–4.69, 3.97)	0.8695
LC - Hemoptysis	–1.06 (–2.25, 0.13)	0.16 (–1.91, 2.23)	–1.22 (–3.60, 1.17)	0.2964
LC - Sore mouth	1.14 (–0.03, 2.31)	2.55 (0.59, 4.51)	–1.41 (–3.70, 0.88)	0.2254
LC - Dysphagia	0.46 (–0.61, 1.53)	–0.15 (–1.89, 1.60)	0.61 (–1.44, 2.65)	0.5611
LC - Peripheral neuropathy	12.31 (9.53, 15.09)	10.04 (5.64, 14.44)	2.27 (–2.94, 7.47)	0.3918
LC - Alopecia	18.19 (15.59, 20.79)	20.70 (16.55, 24.84)	–2.51 (–7.41, 2.39)	0.3149
LC - Pain in chest	–6.38 (–8.43, –4.32)	–4.78 (–8.03, –1.53)	–1.60 (–5.43, 2.24)	0.4137
LC - Pain in arm or shoulder	–1.65 (–3.77, 0.47)	–2.02 (–5.40, 1.36)	0.37 (–3.61, 4.35)	0.8547
LC - Pain in other parts	–0.08 (–2.28, 2.12)	0.17 (–3.42, 3.75)	–0.25 (–4.45, 3.96)	0.9081



Data cut off: 14 June 2021. EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; LC, lung cancer; QLQ-C30, Quality of Life-Core 30 questionnaire; QLQ-LC13, Quality of Life-Lung Cancer Module 13 questionnaire; QoL, quality of life; TTD, time to clinically meaningful deterioration
Source: Baramidze et al, 2024 (supplementary material) (63)

An analysis of time to definitive clinically meaningful deterioration in all function and symptom scales was also performed. Time to definitive clinically meaningful deterioration in GHS/QoL and functioning scales was defined as the time from

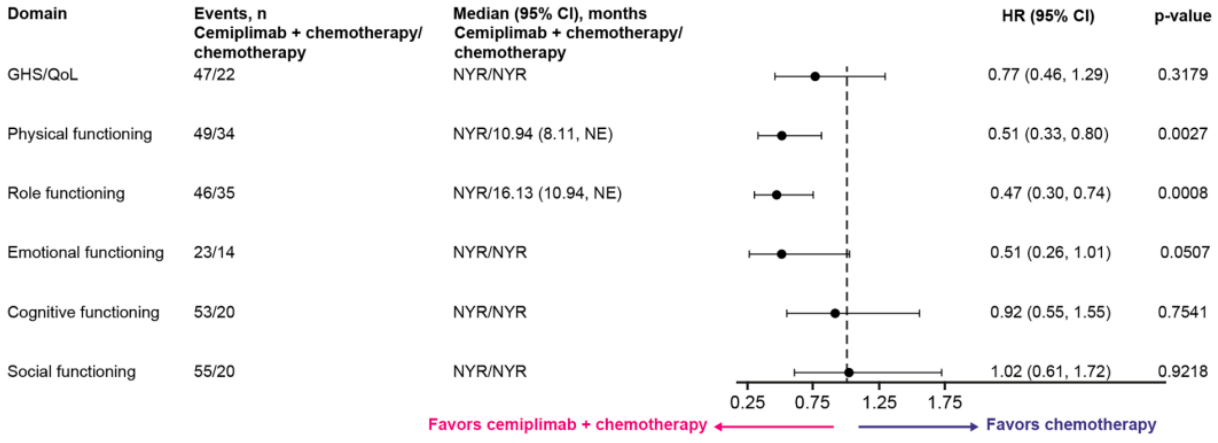
randomization to the first observation with a greater than or equal to 10-point decrease and no subsequent observations with a less than 10-point decrease from baseline or until patient drop-out resulting in missing data. For symptom scales, time to definitive clinically meaningful deterioration was defined as the time from randomization to the first observation with a greater than or equal to 10-point increase and no subsequent observations with a less than 10-point increase from baseline or until patient drop-out resulting in missing data.

There was a delay in time to definitive clinically meaningful deterioration favouring cemiplimab plus chemotherapy in:

- QLQ-C30 functioning: physical functioning, role functioning (Figure 10a)
- QLQ-C30 specific symptoms: nausea/vomiting, pain, dyspnoea (Figure 10b)
- QLQ-LC13 specific symptoms: dyspnoea, coughing, sore mouth, alopecia (Figure 10c)

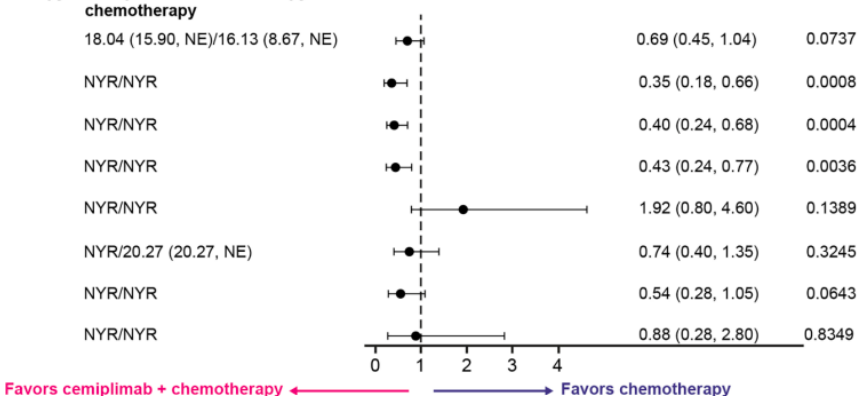
Figure 10 Forest plot for time to definitive clinically meaningful deterioration: EMPOWER Lung-3 MHRA label population (PD-L1 ≥1%)

(a) GHS/QoL and EORTC QLQ-C30 functioning



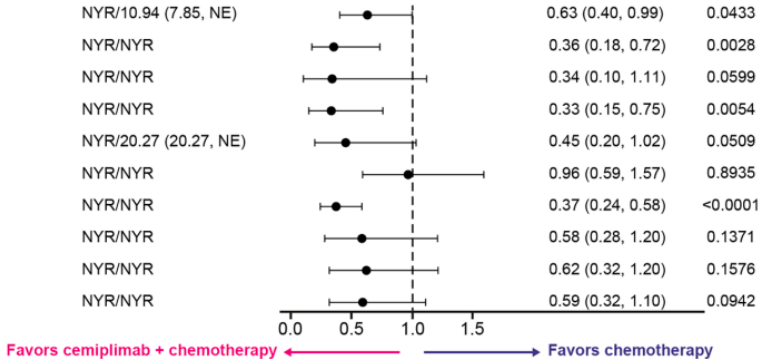
(b) EORTC QLQ-C30 symptoms

Domain	Events, n Cemiplimab + chemotherapy/ chemotherapy	Median (95% CI), months Cemiplimab + chemotherapy/ chemotherapy	HR (95% CI)	p-value
Fatigue	67/35	18.04 (15.90, NE)/16.13 (8.67, NE)	0.69 (0.45, 1.04)	0.0737
Nausea/vomiting	20/19	NYR/NYR	0.35 (0.18, 0.66)	0.0008
Pain	34/27	NYR/NYR	0.40 (0.24, 0.68)	0.0004
Dyspnea	28/21	NYR/NYR	0.43 (0.24, 0.77)	0.0036
Insomnia	34/6	NYR/NYR	1.92 (0.80, 4.60)	0.1389
Appetite loss	33/16	NYR/20.27 (20.27, NE)	0.74 (0.40, 1.35)	0.3245
Constipation	24/15	NYR/NYR	0.54 (0.28, 1.05)	0.0643
Diarrhea	12/4	NYR/NYR	0.88 (0.28, 2.80)	0.8349



(c) EORTC QLQ-LC13 symptoms

Domain	Events, n Cemiplimab + chemotherapy/ chemotherapy	Median (95% CI), months Cemiplimab + chemotherapy/ chemotherapy	HR (95% CI)	p-value
LC - Dyspnoea	55/30	NYR/10.94 (7.85, NE)	0.63 (0.40, 0.99)	0.0433
LC - Coughing	19/15	NYR/NYR	0.36 (0.18, 0.72)	0.0028
LC - Hemoptysis	5/6	NYR/NYR	0.34 (0.10, 1.11)	0.0599
LC - Sore mouth	13/11	NYR/NYR	0.33 (0.15, 0.75)	0.0054
LC - Dysphagia	14/10	NYR/20.27 (20.27, NE)	0.45 (0.20, 1.02)	0.0509
LC - Peripheral neuropathy	55/23	NYR/NYR	0.96 (0.59, 1.57)	0.8935
LC - Alopecia	43/42	NYR/NYR	0.37 (0.24, 0.58)	<0.0001
LC - Pain in chest	22/12	NYR/NYR	0.58 (0.28, 1.20)	0.1371
LC - Pain in arm or shoulder	27/14	NYR/NYR	0.62 (0.32, 1.20)	0.1576
LC - Pain in other parts	29/16	NYR/NYR	0.59 (0.32, 1.10)	0.0942



Data cut off: 14 June 2021. EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; LC, lung cancer; NC, not calculable; NYR, not yet reached; QLQ-C30, Quality of Life-Core 30 questionnaire; QLQ-LC13, Quality of Life-Lung Cancer Module 13 questionnaire; QoL, quality of life
Source: Baramidze et al, 2024 (supplementary material) (63)

B.2.7 Subgroup analysis

EMPOWER-Lung 3 was not powered to evaluate differential effectiveness in subgroups and it should be noted that interpretation of results in some subgroups is limited (e.g. by small patient numbers or by the potential for confounding owing to potential imbalances in prognostic baseline characteristics).

B.2.7.1 Pre-planned subgroup analyses (ITT population)

The following pre-planned subgroup analyses were carried out on OS, PFS and ORR to investigate treatment effects across sub-populations.

- Age (<65 years *vs* ≥65 years)
- Race (white *vs* non-white)
- Gender (male *vs* female)
- Ethnicity (Hispanic/Latino *vs* other)
- Histology (squamous, non-squamous)
- PD-L1 expression levels (<1% *vs* 1% to 49% *vs* ≥50%)
- ECOG status (0 *vs* 1)
- Geographic region of enrolling site (Europe, Asia)
- Brain metastasis (yes, no)
- Liver metastasis (yes, no)
- Stage of disease (locally advanced, metastatic)
- Smoking history (smokers, non-smokers)

OS, PFS and ORR by liver metastases (yes, no) were analysed post-hoc.

All subgroup analyses were exploratory and were not adjusted for multiple comparisons.

Full results of all subgroup analyses are shown in Appendix E. In summary, for OS, there were consistent treatment effects in favour of cemiplimab + chemotherapy across most of the tested subgroups (which represent important patient characteristics, including potential treatment modifiers), including both squamous and non-squamous histology.

Importantly, no overall differences in safety or efficacy were observed between elderly patients and younger patients treated with cemiplimab + chemotherapy (3).

B.2.7.2 NICE decision problem subgroups

The following four subgroups were included in the decision problem (see Table 1):

- Squamous, PD-L1 1-49%
- Squamous, PD-L1 ≥50%
- Non-squamous, PD-L1 1-49%
- Non-squamous, PD-L1 ≥50%

Patient characteristics were broadly similar across the subgroups, with exceptions aligned with what would be expected in routine clinical practice (e.g. a higher proportion of female patients in the non-squamous subgroups) (79). Full details of the patient characteristics in these subgroups are given in Appendix E.

The results of the subgroup analyses are summarised in Table 10. Cemiplimab + chemotherapy had consistent benefit in OS and PFS with a similar magnitude of treatment effect across subgroups. This is in agreement with consistent feedback from UK clinical expert lung oncologists, who said that in their experience, histology and PD-L1 levels do not meaningful impact long-term survival (47). Based on this, the economic model base case for this submission includes both histologies.

Although these analyses are based on small subgroups of subgroups, which means they should be interpreted with caution, the data show a consistent magnitude and direction of treatment effect across subgroups as seen in the full licensed population.

Table 10 Efficacy outcomes in the NICE decision problem subgroups

NICE subgroup	OS			PFS			ORR, %
	Events[a]	Median, months[a]	HR (95% CI)	Events[a]	Median, months[a]	HR (95% CI)	
Squamous							
PD-L1 1-49% (n = 81)	31/53 vs 19/28	23.2 vs 8.6	0.52 (0.29, 0.92)	45/53 vs 25/28	6.7 vs 4.2	0.55 (0.33, 0.90)	43.4 vs 25.0
PD-L1 ≥50% (n = 65)	25/42 vs 15/23	22.2 vs 15.1	0.77 (0.40, 1.45)	33/42 vs 18/23	8.3 vs 5.5	0.51 (0.28, 0.92)	47.6 vs 26.1
Non-squamous							
PD-L1 1-49% (n = 94)	31/61 vs 24/33	23.2 vs 12.0	0.48 (0.28, 0.82)	42/61 vs 30/33	8.5 vs 6.2	0.42 (0.26, 0.69)	42.6 vs 15.2
PD-L1 ≥50% (n = 87)	27/61 vs 19/26	24.8 vs 14.4	0.42 (0.23, 0.76)	37/61 vs 21/26	12.5 vs 5.2	0.46 (0.27, 0.80)	57.4 vs 26.9

[a]Data are cemiplimab + chemotherapy vs placebo + chemotherapy

CI, confidence interval; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival;

Source: Makharadze et al, 2024 (supplementary information) (63)

B.2.8 Meta-analysis

There is only one RCT (EMPOWER-Lung 3) in the target population, therefore a meta-analysis was not conducted.

B.2.9 Indirect and mixed treatment comparisons

Key messages

- There is no direct head-to-head comparison of cemiplimab + chemotherapy with pembrolizumab + chemotherapy in the target population
- UK clinical expert lung oncologists said that they would not expect the outcomes to be any different between the two treatments. In support of this:
    - A side-by side comparison shows that OS and PFS curves are very similar for the two treatments (see Figure 15 and Figure 16 in Section B.3.1.1.1)
    - In a recently published NMA by Liu et al (2023) conducted among patients with any PD-L1 and any histology, cemiplimab + chemotherapy demonstrated comparable results to all IO comparators for OS and PFS (55)
- Regeneron performed a two-step multivariate NMA with the PD-L1 ≥1%, any histology scenario as the base case to align with the MHRA label population
    - The NMA results are associated with uncertainty due to inherent limitations in the publicly available evidence base for the relevant comparator, and wide credible intervals around point estimates
    - Nonetheless, the collective indirect evidence indicates there are no clinically meaningful differences in efficacy and safety outcomes. This is the consistent view of UK clinical experts with experience of use of IO in NSCLC

- NICE has previously noted the lack of statistically significant difference in efficacy based on NMA comparisons between other IOs in advanced/metastatic NSCLC and has consequently considered cost comparison analysis informative for decision making (e.g., atezolizumab vs pembrolizumab; TA705 FAD) (40).

- Other international HTA bodies that evaluate cost-effectiveness, including CADTH and PBAC have acknowledged limitations of the evidence base and NMA approach, and ultimately considered economic analysis assuming equivalent efficacy for cemiplimab + chemotherapy and IO + chemotherapy comparators (e.g., pembrolizumab + chemotherapy) to be a more relevant basis for decision making (80, 81).

- It is therefore reasonable to conclude that all available evidence strongly indicates that there are no meaningful differences in the clinical effectiveness of cemiplimab + chemotherapy and pembrolizumab + chemotherapy.

B.2.9.1 Methods of the NMA

A network meta-analysis (NMA) was carried out to evaluate the comparative efficacy and safety of cemiplimab + chemotherapy vs. NICE-recommended comparators (pembrolizumab + chemotherapy; pembrolizumab monotherapy; atezolizumab + bevacizumab + carboplatin + paclitaxel; atezolizumab monotherapy) as a first-line treatment for patients with advanced or metastatic NSCLC. Full details of the methods are given in Appendix D. Briefly:

- Relevant RCTs were identified through the SLR described in Appendix D

- A feasibility assessment was performed to determine if an NMA could be conducted and what issues may affect the validity and interpretation of the results

- Due to violations in the assumption of proportional hazards (PH) (Appendix D), a two-step multivariate NMA was performed based on the methods outlined by Cope et al., 2020 (82). This involved fitting the seven standard parametric distributions for each arm of each trial (i.e., Weibull, Gompertz, log-normal, log-logistic, exponential, gamma, generalized gamma) and then synthesizing the parameters of these distributions using the multivariable NMA framework. This approach has been considered appropriate in previous NICE NSCLC TAs (TA584, TA705, TA760), and was the planned approach of the EAG leading development of NICE NSCLC pathway pilot (10).

The SLR identified 10 RCTs that were suitable for inclusion in the NMA (see Appendix D). The feasibility assessment focussed on 10 scenarios defined by PD-L1 status and histology (Table 11). Of these, the PD-L1 ≥1%, any histology scenario was considered the efficacy base case as it aligns with the MHRA label population. This scenario is the focus of this submission, with the four key decision problem subgroup scenarios presented in Appendix D. The remaining scenarios are not relevant to the decision problem and are not described further.

Table 11 Scenarios included in the NMA

Base case analyses
PD-L1 ≥1%, any histology (efficacy base-case; aligned with cemiplimab MHRA label)
Any PD-L1, any histology (safety base-case)
Key decision problem subgroup analyses
PD-L1 1-49%, squamous histology
PD-L1 ≥50%, squamous histology
PD-L1 1-49%, non-squamous histology
PD-L1 ≥50%, non-squamous histology
Additional decision problem subgroup analyses by only PD-L1 expression level or histology
PD-L1 ≥1%, squamous histology
PD-L1 ≥1%, non-squamous histology
PD-L1 1-49%, any histology
PD-L1 ≥50%, any histology

PD-L1; programmed death ligand 1

For this submission, the comparison of interest is cemiplimab + chemotherapy vs pembrolizumab + chemotherapy. Of the 10 studies identified, 4 were relevant to the base case analyses for this comparison (Table 12).

Table 12 Summary of trials used in the NMA base case analyses

	Cemi + IC chemo	Pembro + IC chemo	Pembro + carbo + pem	IC chemo	Carbo + pem
EMPOWER-Lung 3	Yes			Yes	
KEYNOTE-021G			Yes		Yes
KEYNOTE-189		Yes		Yes	
KEYNOTE-407		Yes		Yes	

Carbo, carboplatin; cemi, cemiplimab; chemo, chemotherapy; IC, investigator's choice; pem, pemetrexed; pembro, pembrolizumab
Source: Data on file: Cemiplimab + chemotherapy NMA report (83)

Figure 11 shows network diagrams for the base-case efficacy analyses for cemiplimab + chemotherapy vs pembrolizumab + chemotherapy in the PD-L1 ≥1% any histology population aligned with the MHRA label for cemiplimab. Figure 12 shows network diagrams for the base-case safety analyses for cemiplimab + chemotherapy vs pembrolizumab vs chemotherapy in the any PD-L1 and any histology population. Network diagrams for all other scenarios are included in Appendix D.

Figure 11 Network diagrams for the base case efficacy analyses

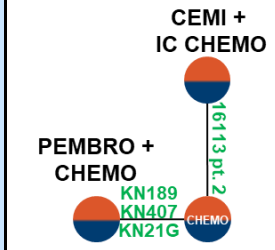
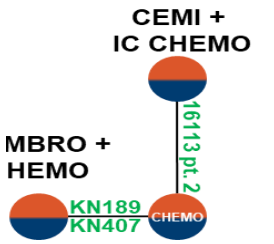
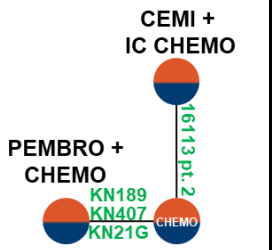
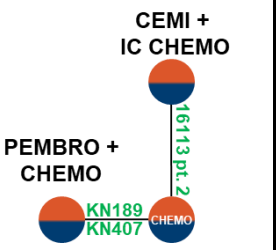
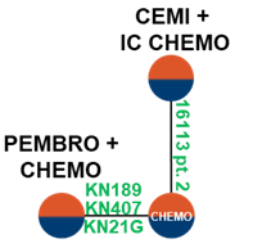
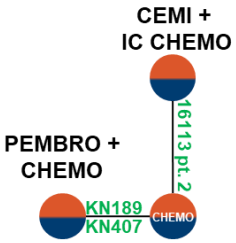
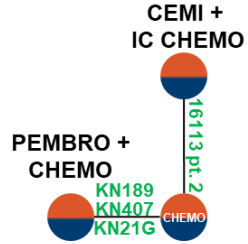
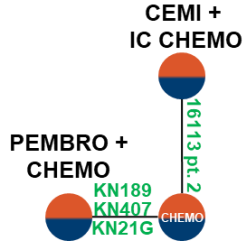
Scenario	Overall survival		Progression-free survival		ORR
	Constant HR	Time-varying HR	Constant HR	Time-varying HR	
PD-L1 ≥1%, any histology (efficacy base case)					

Figure 12 Network diagrams for the base case safety analyses

Scenario	Safety		
	Grade 3 to 5 all-cause AEs	Grade 3 to 5 IMAEs	DAEs
Any PD-L1, any histology (safety base case)			

The feasibility assessment identified areas of meaningful uncertainty, which must be considered when interpreting the results of the NMA. These were:

Assumption of similarity in treatment effect modifiers

Baseline characteristics were not reported in the target population for any comparator trial across most scenarios (including the PD-L1 ≥1%, any histology scenario), therefore similarity in potential treatment effect modifiers had to be assumed.

Small number of direct comparisons in the networks

There were a small number of trials per direct comparison in the networks, with each pair of interventions informed by only one to three trials. This resulted in a relatively small amount of data being available for each comparison and, consequently, the estimated HRs had greater uncertainty (wider credible intervals [CrIs]). In addition, the use of subgroup level data from EMPOWER Lung-3 and most comparator trials for the PD-L1 and histology-specific scenarios resulted in a reduction in sample size and statistical power.

Limited reporting of crossover-adjusted results

At least one trial in each scenario permitted on-study crossover, but there was limited reporting of crossover-adjusted OS results, so sensitivity analyses accounting for crossover were not considered. Differences in crossover design between studies poses a risk of bias, as treatment switching can lessen the observed treatment effects relative to what would have been seen if no switching took place. This imposes an important limitation on the OS NMA for any scenario performed without using cross-over adjusted data.

Limited reporting of subsequent immunotherapy

Rates of subsequent immunotherapy off study were not reported for the target population of interest in any comparator trials for most scenarios (including the PD-L1 ≥1%, any histology scenario), so the impact of any difference could not be assessed.

B.2.9.2 Results of the NMA

This section focuses on the base-case analyses for cemiplimab + chemotherapy vs pembrolizumab vs chemotherapy in the PD-L1 ≥1% and any histology population aligned with the MHRA label. Results of the four key decision problem subgroup analyses were consistent with the base case and are provided in Appendix D. Results for all other scenarios can be found in the NMA technical report (83). Results for cemiplimab + chemotherapy vs pembrolizumab + chemotherapy were not impacted by use of a restricted (i.e. pembrolizumab + chemotherapy only) vs a wider (including other comparators) network.

B.2.9.2.1 Efficacy

Table 13 shows a top-level overview of the results of the efficacy analyses. Note that fixed effect models were preferred for all analyses. It was not feasible to estimate the heterogeneity parameter of a random effect model because all evidence networks consisted of relatively few trials and therefore led to unstable estimates. However, sensitivity analyses were performed using random effects models with informative priors for between study heterogeneity; the results were consistent with the base case (see the full NMA report for details (83)).

In the base case time-varying HR NMA of patients with PD-L1 ≥1% and any histology (i.e. the MHRA label population), the point estimates were close to 1 with 95% CrIs spanning 1 for all outcomes at all timepoints, indicating comparable efficacy with no statistically significant differences between cemiplimab + chemotherapy vs pembrolizumab + chemotherapy.

Sensitivity analyses using constant HRs were generally consistent with the base case for OS and PFS. A further sensitivity analysis was carried out that excluded KEYNOTE-021G owing to differences with the other trials in terms of location (the study was only conducted in two countries) and sample size (as a phase 2 study, KEYNOTE-021G enrolled fewer patients than the other trials). The results were consistent with the base-case. The results of the sensitivity analyses can be found in the NMA report (83).

Table 13 Top-level summary of efficacy NMA results for the PD-L1 ≥1%, any histology (MHRA label population) scenario (fixed effect model)

Scenario	Trials included	Comparator	Efficacy profile of cemiplimab + chemotherapy versus comparators				
			Overall survival		Progression-free survival		ORR
			Time-varying HR	Constant HR	Time-varying HR	Constant HR	
PD-L1 ≥1%, any histology[a] *Base case*	• R2810-ONC-16113 pt.2 (subgroup; PD-L1 ≥1%, any histology) • KEYNOTE-021G (subgroup; PD-L1 ≥1%, non-sq.; OS/PFS constant HR only) • KEYNOTE-189 (subgroup; PD-L1 ≥1%, non-sq.) • KEYNOTE-407 (subgroup; PD-L1 ≥1%, sq.)	Pembro + chemo					
PD-L1 ≥1%, any histology *Sensitivity analysis excluded KEYNOTE-021G[a]*	• R2810-ONC-16113 pt.2 (subgroup; PD-L1 ≥1%, any histology) • KEYNOTE-021G (subgroup; PD-L1 ≥1%, non-sq.; OS/PFS constant HR only) • KEYNOTE-189 (subgroup; PD-L1 ≥1%, non-sq.) • KEYNOTE-407 (subgroup; PD-L1 ≥1%, sq.)	Pembro + chemo	(same as base case)		(same as base case)		NA

Results from time-varying HR NMAs consider the best-fitting model. Light green indicates results were comparable (not statistically significant at all timepoints) with point estimates in favour of cemi + chemo; Orange indicates results were comparable (not statistically significant at all timepoints) with point estimates in favour of comparator Based on EMPOWER-Lung 3 part 2, June 2022 data cut-off. **a)** Efficacy analyses used most mature data from peer-reviewed full-text publications.
Cemi, cemiplimab; Chemo, chemotherapy; HR, hazard ratio; NA, not applicable; NMA, network meta-analysis; Non-sq, non-squamous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; PFS, progression-free survival; Sq, squamous.

Overall survival

Table 14 shows the point estimates and 95% CrIs for the base case analysis of OS.

Table 14 OS NMA results for the PD-L1 ≥1%, any histology scenario (log-logistic, fixed effect model)

Cemiplimab + chemotherapy vs.	Time-varying HR (95% CrI)							
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Pembrolizumab + chemotherapy	0.94 (0.52, 1.57)	0.90 (0.60, 1.32)	0.88 (0.62, 1.26)	0.87 (0.62, 1.26)	0.87 (0.61, 1.28)	0.87 (0.60, 1.30)	0.88 (0.60, 1.31)	0.88 (0.60, 1.32)

Cells shaded in light grey indicate timepoint past shortest median follow-up of treatments included in a given comparison; cells shaded in dark grey indicate estimates based on model extrapolations. The model presented is log-logistic, fixed-effect. All bolded values are statistically significant at the 0.05 significance level.
CrI, credible interval; HR, hazard ratio.

Progression-free survival

Table 15 shows the point estimates and 95% CrIs for the base case analysis of PFS.

Table 15 PFS NMA results for the PD-L1 ≥1%, any histology scenario (log-logistic, fixed effect model)

Cemiplimab + chemotherapy vs.	Time-varying HR (95% CrI)							
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Pembrolizumab + chemotherapy	1.09 (0.77, 1.53)	1.06 (0.79, 1.45)	1.04 (0.76, 1.45)	1.03 (0.74, 1.45)	1.02 (0.72, 1.43)	1.01 (0.72, 1.42)	1.00 (0.72, 1.40)[a]	1.00 (0.72, 1.38)[b]

Cells shaded in light grey indicate timepoint past shortest median follow-up of treatments included in a given comparison; cells shaded in dark grey indicate estimates based on model extrapolations. Model presented is log-logistic, fixed-effect. All bolded values are statistically significant at the 0.05 significance level. a) HR 1.0044 (95% CrI 0.7202, 1.3957); b) HR 1.0010, 95% CrI 0.7229, 1.3804

CrI, credible interval; HR, hazard ratio

Objective response rate

The OR from the fixed-effect NMA of ORR among patients with PD-L1 ≥1%, any histology for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy was 1.09 (95% CrI: 0.60, 2.00).

B.2.9.2.2 Safety

Table 16 shows a top-level overview of the results of the safety analyses.

Cemiplimab + chemotherapy was associated with a comparable incidence of Grade 3 to 5 all-cause AES, grade 3 to 5 immune-mediated AEs and discontinuations due to all-cause AEs versus pembrolizumab + chemotherapy.

Table 16 Top-line summary of safety NMA results for any PD-L1, any histology scenario

Scenario	Trials included	Comparator	Safety profile of cemiplimab + chemotherapy versus comparators		
			Grade 3 to 5 all-cause AEs	Grade 3 to 5 IMAEs	DAEs
Any PD-L1, any histology	• R2810-ONC-16113 pt.2 (as-treated; any PD-L1, any histology) • KEYNOTE-021G (as-treated; any PD-L1, non-sq.; IMAEs & DAEs only) • KEYNOTE-189 (as-treated; any PD-L1, non-sq.) • KEYNOTE-407 (as-treated; any PD-L1, sq.)	Pembro + chemo			

Light green indicates results were comparable (not statistically significant at all timepoints) with point estimates in favour of cemi + chemo; Orange indicates results were comparable (not statistically significant at all timepoints) with point estimates in favour of comparator; Based on EMPOWER-Lung 3 part 2, June 2022 data cut-off. Safety analyses used data from follow-up duration from each trial that was most similar to the follow-up duration in EMPOWER-Lung 3 part 2 (i.e., median 28.4 months for safety analysis set).

AE, adverse event; Cemi, cemiplimab; Chemo, chemotherapy; DAEs, discontinuations due to all-cause adverse events; IMAEs, immune-mediated adverse events; NMA, network meta-analysis; Non-sq, non-squamous; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; Sq, squamous.

Table 17 shows the ORs and 95% CrIs from the base case safety NMAs.

Table 17 Safety NMA results for the any PD-L1, any histology scenario (fixed effect)

Cemiplimab + chemotherapy vs.	OR (95% CrI)		
	Grade 3 to 5 all-cause AEs	Grade 3 to 5 IMAEs	DAE
Pembrolizumab + chemotherapy	1.53 (0.95, 2.49)	1.58 (0.27, 9.78)	0.55 (0.22, 1.50)

AE, adverse event; CrI, credible interval; DAE, discontinuation due to all-cause AEs; IMAE, immune-mediated AE; NMA, network meta-analysis; OR, odds ratio

B.2.9.3 NMA conclusions

UK clinical expert lung oncologists consulted during development of this submission have consistently fed back that they would not expect outcomes to differ between cemiplimab + chemotherapy and pembrolizumab + chemotherapy. This appears to be supported by a side-by side comparison of the trial data, which show OS and PFS outcomes to be very similar (see Figure 15 and Figure 16 in Section B.3.1.1.1) and by the results of a recently published NMA (Liu et al., 2023) conducted among patients with any PD-L1 and any histology, in which cemiplimab + chemotherapy demonstrated comparable results to all IO comparators for OS and PFS (55). However, the NMA by Liu et al was subject to some limitations as it included trials regardless of PD-L1 expression or histology, and did not assess the PH assumption or consider time-varying HRs as an alternative analysis.

Regeneron conducted an NMA to help address some of the limitations of the Liu 2023 analyses, by focusing on trials with PDL1>1% and using a two-step multivariate approach with time varying hazards to account for instances where proportional hazards may not hold. This reached the same conclusions - there were no clinically meaningful or statistically significant differences observed in PFS or OS (or ORR or Grade 3 AEs or discontinuations due to AEs) between cemiplimab + chemotherapy and pembrolizumab + chemotherapy. However, we acknowledge there are still some limitations in the analysis (see Section B.2.9.1) that, together with the consistently wide credible intervals and the broader limitations of the NMA may preclude definitive conclusions about the relative efficacy of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy.

Of note, NICE has previously noted the lack of statistically significant difference in efficacy based on NMA comparisons between other IOs in advanced/metastatic NSCLC and has consequently considered cost comparison analysis informative for decision making (e.g., atezolizumab vs pembrolizumab; TA705 FAD) (40). In addition, other international HTA bodies that evaluate cost-effectiveness, including CADTH and PBAC, have acknowledged limitations of the evidence base and NMA approach, and ultimately considered economic analysis assuming equivalent efficacy for cemiplimab + chemotherapy and IO + chemotherapy comparators (e.g., pembrolizumab + chemotherapy) to be a more relevant basis for decision making (80, 81).

It is therefore reasonable to conclude that all available evidence strongly indicates that there are no meaningful differences in the clinical effectiveness of cemiplimab + chemotherapy and pembrolizumab +chemotherapy.

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

A number of uncertainties were identified that must be taken into consideration when interpreting the results of the NMA; a description of these, and how they may have affected the results of the NMA is given in Section B.2.9.1. Whilst these limitations may potentially lead to bias in OS estimates, this in itself would not be expected to influence estimates of relative treatment effects for progression-based outcomes, and our analyses indicate that there are no meaningful differences between cemiplimab + chemotherapy and pembrolizumab + chemotherapy for progression-based outcomes.

B.2.10 Adverse reactions

Data presented in this section are from the 2-year follow-up of EMPOWER-Lung 2 (data cut off 14 June 2022). Results are reported for the overall EMPOWER-Lung 3 study population, as safety outcomes are not expected to be impacted by PD-L1 expression. Safety results for the MHRA label population (PD-L1 ≥1%) are presented in Appendix O.

Key messages:

- No new safety signals were identified at the 2-year follow-up of EMPOWER-Lung 3.
    - The safety profile for cemiplimab + chemotherapy was generally similar to that previously reported for other IO + chemotherapy regimens (16, 84, 85), and was considered by the EMA to be acceptable considering the treated and targeted disease of advanced lung cancer (58).
- Cemiplimab + chemotherapy was broadly well tolerated with limited incremental toxicity compared with placebo + chemotherapy
- Events such as anaemia, nausea and hyperglycaemia were more common with cemiplimab + chemotherapy than with placebo + chemotherapy
    - However, these events are common with IO + chemotherapies
    - No additional safety/toxicity concerns were identified vs existing IO + chemotherapy options
- Grade ≥3 TEAEs occurred in 48.7% of patients treated with cemiplimab + chemotherapy *vs* 32.7% treated with placebo + chemotherapy
- Few patients discontinued treatment with cemiplimab + chemotherapy because of TEAEs (6.1% *vs* 4.6% with placebo + chemotherapy)
- Sponsor-identified immune-related TEAEs occurred in 18.9% of patients receiving cemiplimab + chemotherapy
    - Rates of pneumonitis (1.6%), nephritis (0.3%), colitis (0.3%) and rash (6.3%) were low in the context of rates previously reported in other IO + chemotherapy studies
- The cumulative exposure from post-marketing experience is estimated at 52,273 patient years; the risk-benefit profile remains positive

- The potential for chemo-flexibility with cemiplimab + chemotherapy (see Section B.1.3.8) may allow better patient management to minimise toxicities

B.2.10.1 Treatment-emergent AEs

The overall incidence of TEAEs was similar between treatment groups (Table 18), with a greater incidence of Grade 3 to 5 events in the cemiplimab + chemotherapy group.

The incidence of TEAEs leading to discontinuation was low in both treatment groups. The most common TEAEs leading to discontinuation of cemiplimab + chemotherapy were anaemia (n = 3 [1.0%]) and ALT increased (n = 2 [0.6%]).

Twenty-seven patients (8.7%) receiving cemiplimab + chemotherapy had TEAEs that led to death, compared with 14 (9.2%) in the placebo + chemotherapy group. The most common TEAEs leading to death in both treatment groups were death (9 patients [2.9%] in the cemiplimab + chemotherapy group and 2 [1.3%] in the placebo + chemotherapy group) and pulmonary embolism in the placebo + chemotherapy group (4 patients [1.3%] in the cemiplimab + chemotherapy group and 2 [1.3%] in the placebo + chemotherapy group).

Ninety-four patients (30.1%) in the cemiplimab + chemotherapy group and 37 (24.2%) in the placebo + chemotherapy group had serious AEs (SAEs). The most common SAEs were pneumonia, anaemia and death in the cempilimab + chemotherapy group (each n = 9 [2.9%]) and febrile neutropenia (n = 4 [2.5%]) in the placebo + chemotherapy group.

Table 18 Summary of TEAEs (safety population)

Event, n (%) of patients	Cemiplimab + chemotherapy (n = 312)		Placebo + chemotherapy (n = 153)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	301 (96.5)	152 (48.7)	145 (94.8)	50 (32.7)
TEAE leading to death	27 (8.7)	27 (8.7)	14 (9.2)	14 (9.2)
TEAE leading to discontinuation	19 (6.1)	15 (4.8)	7 (4.6)	4 (2.6)
TEAE occurring in ≥10% of patients in either group				
Anaemia	143 (45.8)	34 (10.9)	61 (39.9)	10 (6.5)
Alopecia	116 (37.2)	0	67 (43.8)	0
Nausea	79 (25.3)	0	25 (16.3)	0
Hyperglycaemia	57 (18.3)	6 (1.9)	18 (11.8)	0
ALT increased	55 (17.6)	8 (2.6)	23 (15.0)	3 (2.0)
Decreased appetite	55 (17.6)	4 (1.3)	19 (12.4)	0
Arthralgia	50 (16.0)	2 (0.6)	20 (13.1)	0
AST increased	50 (16.0)	1 (0.3)	19 (12.4)	3 (2.0)
Neutropenia	50 (16.0)	20 (6.4)	19 (12.4)	9 (5.9)
Constipation	44 (14.1)	1 (0.3)	17 (11.1)	0
Fatigue	44 (14.1)	9 (2.9)	12 (7.8)	1 (0.7)
Thrombocytopenia	43 (13.8)	10 (3.2)	19 (12.4)	2 (1.3)
Asthenia	42 (13.5)	7 (2.2)	18 (11.8)	2 (1.3)
Dyspnea	42 (13.5)	8 (2.6)	10 (6.5)	1 (0.7)
Blood creatinine increased	39 (12.5)	3 (1.0)	9 (5.9)	0
Vomiting	39 (12.5)	0	15 (9.8)	0
Weight decreased	39 (12.5)	4 (1.3)	13 (8.5)	0
Insomnia	36 (11.5)	0	11 (7.2)	0
Diarrhoea	35 (11.2)	4 (1.3)	10 (6.5)	0
Hypoalbuminemia	34 (10.9)	2 (0.6)	10 (6.5)	0

ALT, alanine aminotransferase ; AST aspartate aminotransferase ; TEAE, treatment-emergent adverse event

Source: Makharadze et al 2023, erratum (61)

B.2.10.2 Treatment-related AEs

Table 19 summarises treatment-related AEs. The overall incidence of treatment-related AEs was similar between treatment groups, with a greater incidence of Grade 3 to 5 events in the cemiplimab + chemotherapy group. The most common (reported in ≥15% of patients) treatment-related AEs in the cemiplimab + chemotherapy group were anaemia, alopecia, nausea, ALT increased and neutropenia. In the placebo + chemotherapy group, the most common treatment-related AEs were alopecia, anaemia and nausea.

Four patients (1.3%) receiving cemiplimab + chemotherapy had treatment-related AEs that led to death (death, general physical health deterioration, mesenteric artery thrombosis and pneumonitis). One patient (0.7%) in the placebo + chemotherapy group had a treatment-related AE that led to death (enterocolitis). The EPAR states that *"the narratives for these deaths have been reviewed and it is agreed that there was only one death related to treatment with cemiplimab in this safety population; i.e. the one patient (0.3%) who died from pneumonitis"* (58).

Forty-nine patients (15.7%) in the cemiplimab + chemotherapy group had treatment-related SAEs, compared with 15 (9.8%) in the placebo + chemotherapy group. The most commonly-reported treatment-related SAEs in the cemiplimab + chemotherapy group were anaemia (8 patients [2.6%]), febrile neutropenia (4 patients [1.3%] and neutropenia (3 patients [1.3%]). In the placebo + chemotherapy group, the most commonly reported treatment-related SAEs were febrile neutropenia (4 patients [2.6%]) and anaemia (2 patients [1.3%]).

Table 19 Summary of treatment-related AEs (safety population)

Event, n (%) of patients	Cemiplimab + chemotherapy (n = 312)		Placebo + chemotherapy (n = 153)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any treatment-related AE	276 (88.5)	94 (30.1)	131 (85.6)	28 (18.3)
Leading to death	4 (1.3)	4 (1.3)	1 (0.7)	1(0.7)
Leading to discontinuation	13 (4.2)	9 (2.9)	2 (1.3)	1 (0.7)
Anaemia	131 (42.0)	33 (10.6)	52 (34.0)	10 (6.5)
Alopecia	115 (36.9)	0	66 (43.1)	0
Nausea	72 (23.1)	0	25 (16.3)	0
ALT increased	49 (15.7)	6 (1.9)	20 (13.1)	1 (0.7)
Neutropenia	47 (15.1)	18 (5.8)	19 (12.4)	9 (5.9)
AST increased	43 (13.8)	1 (0.3)	16 (10.5)	1 (0.7)
Decreased appetite	43 (13.8)	1 (0.3)	17 (11.1)	0
Thrombocytopenia	39 (12.5)	7 (2.2)	19 (12.4)	1 (0.7)
Vomiting	34 (10.9)	0	14 (9.2)	0
Blood creatinine increased	33 (10.6)	1 (0.3)	8 (5.2)	0
Hyperglycaemia	33 (10.6)	2 (0.6)	13 (8.5)	0
Arthralgia	30 (9.6)	1 (0.3)	11 (7.2)	0
Asthenia	29 (9.3)	2 (0.6)	10 (6.5)	1 (0.7)
Constipation	29 (9.3)	0	12 (7.8)	0
Fatigue	29 (9.3)	3 (1.0)	9 (5.9)	1 (0.7)
Insomnia	29 (9.3)	0	8 (5.2)	0
Peripheral sensory neuropathy	29 (9.3)	0	15 (9.8)	0
Diarrhoea	28 (9.0)	3 (1.0)	4 (2.6)	0
Hypothyroidism	25 (8.0)	1 (0.3)	3 (2.0)	0
White blood cell count decreased	23 (7.4)	10 (3.2)	5 (3.3)	2 (1.3)
Blood urea increased	22 (7.1)	0	6 (3.9)	0
Blood lactate dehydrogenase increased	20 (6.4)	0	5 (3.3)	0

Event, n (%) of patients	Cemiplimab + chemotherapy (n = 312)		Placebo + chemotherapy (n = 153)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypoalbuminaemia	19 (6.1)	0	5 (3.3)	0
Hypokalaemia	19 (6.1)	3 (1.0)	4 (2.6)	1 (0.7)
Platelet count decreased	19 (6.1)	4 (1.3)	6 (3.9)	0
Amylase increased	18 (5.8)	1 (0.3)	5 (3.3)	1 (0.7)
Leukopenia	18 (5.8)	5 (1.6)	10 (6.5)	2 (1.3)
Neuropathy peripheral	18 (5.8)	0	6 (3.9)	0
Weight decreased	18 (5.8)	0	6 (3.9)	0
Blood alkaline phosphatase increased	17 (5.4)	0	10 (6.5)	0
Rash	17 (5.4)	1 (0.3)	4 (2.6)	0
Weight increased	16 (5.1)	0	0	0

AE, adverse event ; ALT, alanine aminotransferase ; AST aspartate aminotransferase

Source: Makharadze et al 2023 (supplementary material) (60)

B.2.10.3 Immune-related AEs

Sponsor-identified immune-related AEs are shown in Table 20. Overall, 18.9% of patients receiving cemiplimab + chemotherapy had immune-related AEs, with 2.9% having events of Grade 3 or above. Three patients (1.0%) discontinued cemiplimab + chemotherapy and one patient died owing to immune-related AEs.

Table 20 Summary of immune-related AEs (safety population)

Event, n (%) of patients	Cemiplimab + chemotherapy (n = 312)	
	Any grade	Grade ≥3
Any	59 (18.9)	9 (2.9)
Leading to death	1 (0.3)	1 (0.3)
Leading to discontinuation	3 (1.0)	3 (1.0)
Hypothyroidism	25 (8.0)	1 (0.3)
Hyperthyroidism	15 (4.8)	0

Blood thyroid-stimulating hormone increased	13 (4.2)	0
Blood thyroid-stimulating hormone decreased	5 (1.6)	0
Pneumonitis	5 (1.6)	1 (0.3)
ALT increased	2 (0.6)	2 (0.6)
Dermatitis	2 (0.6)	0
Pruritus	2 (0.6)	0
Rash	2 (0.6)	1 (0.3)
AST increased	1 (0.3)	0
Autoimmune arthritis	1 (0.3)	0
Autoimmune thyroiditis	1 (0.3)	0
Blood bilirubin increased	1 (0.3)	1 (0.3)
Blood creatinine increased	1 (0.3)	0
Colitis	1 (0.3)	1 (0.3)
Diabetes mellitus	1 (0.3)	0
Gamma-glutamyl transferase increased	1 (0.3)	1 (0.3)
Hypophysitis	1 (0.3)	0
Immune-mediated lung disease	1 (0.3)	1 (0.3)
Immune-related nephritis	1 (0.3)	0
Immune-related thyroiditis	1 (0.3)	0
Psoriasis	1 (0.3)	1 (0.3)
Rash maculopapular	1 (0.3)	1 (0.3)

AE ; adverse event ; ALT, alanine aminotransferase ; AST aspartate aminotransferase

Source: Makharadze et al 2023, (supplementary information) (60)

B.2.10.4 AEs of special interest

AEs of special interest (AESIs), such as anaphylaxis or hypersensitivity, were based on investigator assessment using case report form (CRF) collected criteria. Overall, the incidence of AESIs was low (Table 21). The most frequent treatment-emergent AESI in the cemiplimab + chemotherapy group was grade ≥3 immune-mediated AEs, which occurred in 1.6% of patients (compared with 0.7% in the placebo + chemotherapy group).

Table 21 AEs of special interest (safety population)

AESI	Number (%) of patients	
	Cemiplimab + chemo (n = 312)	Placebo + chemo (n = 153)
Any treatment-emergent AESI	12 (3.8)	5 (3.3)
Grade ≥2 infusion-related reactions	4 (1.3)	3 (2.0)
Grade ≥2 allergic/hypersensitivity reactions	2 (0.6)	0 (0)
Grade ≥3 immune-mediated AEs	5 (1.6)	1 (0.7)

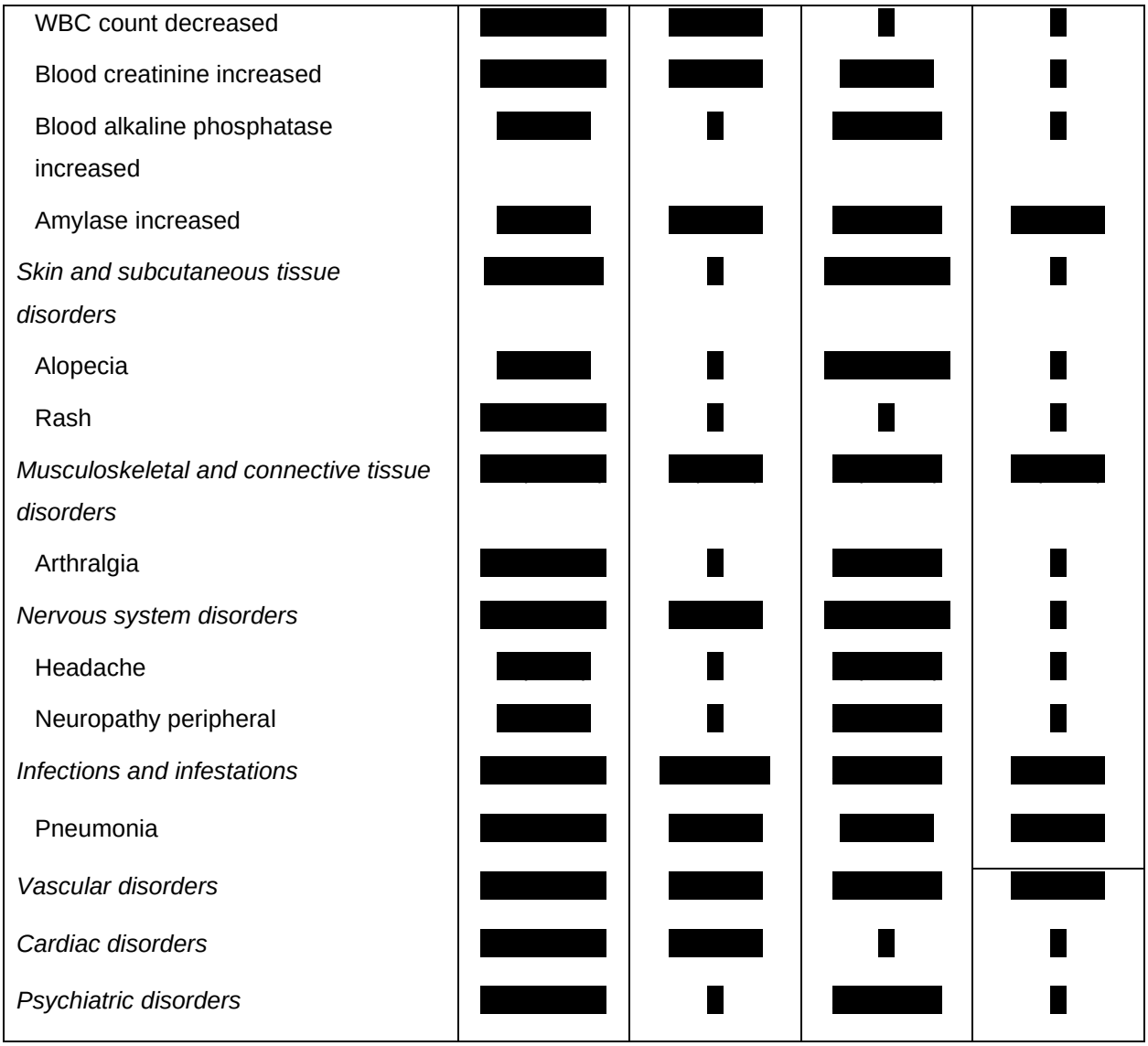
AE, adverse event; AESI, adverse event of special interest
Source: EMPOWER Lung-3 CSR (86)

B.2.10.5 TEAEs with pemetrexed vs paclitaxel (non-squamous histology)

Post-hoc exploratory analyses were conducted to evaluate selected AEs reported for patients with non-squamous histology who received pemetrexed vs paclitaxel-containing regimens (Table 22). While acknowledging the limitations of such analyses, the data suggest the two treatments have a distinct AE profile that will allow clinicians to choose between them based on the comorbidity profile of their patients.

Table 22 TEAEs: pemetrexed and paclitaxel (non-squamous histology)

Event, n (%) of patients	Pemetrexed (n = 114)		Paclitaxel (n = 39)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs in ≥10% of patients (either group)				
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]



ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; WBC, white blood cell
Source: Regeneron data on file: pemetrexed vs paclitaxel (87)

B.2.10.6 Post-marketing experience

At the time of database lock for the latest Periodic Safety Update (27 March 2024), the cumulative exposure to cemiplimab from post-marketing experience in CSCC, basal cell carcinoma, NSCLC and cervical cancer was estimated at 52,273 patient years. At this time, the risk-benefit ratio remains positive.

B.2.11 Ongoing studies

The prespecified final OS analysis of EMPOWER-Lung 3 is complete and the trial was stopped early due to the highly significant improvement in OS for cemiplimab + chemotherapy versus chemotherapy alone. Additional long-term follow-up from the EMPOWER-Lung 3 RCT could potentially become available over the next 12-18 months. However, this is unlikely to change the conclusions given the maturity of the OS and PFS data from the final data cut, and is not anticipated to address the meaningful limitations of the NMA used to inform comparative clinical efficacy for cemiplimab + chemotherapy versus the relevant comparator for this appraisal (i.e., pembrolizumab + chemotherapy) in the cost-utility analysis described in Section B.3.

Cemiplimab is currently being evaluated across a range of solid tumour indications, including as a combination therapy with the LAG-3 inhibitor, fianlimab (initial data expected 2H 2024).

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Strengths and limitations of the clinical evidence base

Strengths

EMPOWER-Lung 3 included historically under-represented, difficult-to-treat patients, such as those with pre-treated and stable brain metastases and locally advanced disease, making the study population representative of clinical practice. It also included a higher proportion of patients with ECOG PS1 than either of the KEYNOTE registrational studies for pembrolizumab + chemotherapy (84.3% vs 56.0% in KEYNOTE-189 and 70.8% in KEYNOTE-407). EMPOWER-Lung 3 is the first study to include patients with both locally advanced NSCLC and metastatic NSCLC as well as patients with both non-squamous and squamous histology.

The outcomes used in EMPOWER-Lung 3 are consistent with those used in UK clinical practice (47) and in previous technology appraisals of IO + chemotherapies in NSCLC (38-40, 43). The primary endpoint was OS, which is a direct measure of clinical benefit to patients, is considered unambiguous, objective and clinically significant, and is recommended by the FDA as the standard clinical benefit endpoint in advanced and metastatic NSCLC (88).

There was no cross-over in EMPOWER-Lung 3, which means the OS results are not subject to cross-over confounding.

Limitations

There are no head-to-head trials of cemiplimab + chemotherapy vs relevant comparators. Therefore a NMA was performed, the results of which show meaningful uncertainty due to inherent limitations in the available evidence base (see Section B.2.9).

At present, EMPOWER-Lung 3 only has 2-year follow up data available, whereas 5-years of follow-up data are available for the registrational pembrolizumab + chemotherapy KEYNOTE studies.

The submission focuses on the PD-L1 ≥1% population from EMPOWER Lung-3 (i.e. the licensed population), but the study was powered for the ITT population. Statistical analyses of the PD-L1 ≥1% population (which comprised approximately 70% of the ITT population) were exploratory and any P-values presented should therefore be considered nominal.

Most patients in EMPOWER-Lung 3 were enrolled in Central and Eastern Europe, which may raise questions about generalizability to the UK patient population. However, UK clinical expert lung oncologists consulted during development of this submission have said that the baseline characteristics of patients enrolled in the study were broadly similar to those of patients they would see in UK clinical practice, and that results from control arms with chemotherapy are generalizable to UK clinical practice and comparable to the KEYNOTE studies, indicating that patients had a similar standard of care.

Results from the EORTC questionnaires may have over-represented patients who did well in both treatment arms as those who progressed no longer completed the questionnaire. Also, differences in baseline scores were compared with published reference values, which may limit generalizability to real-world patients with NSCLC (62).

The PD-L1 assay used in EMPOWER LUNG-3 (Ventana SP263) differed from that used in the pembrolizumab KEYNOTE studies (22C3 pharmDX platform). However, both are currently used in UK clinical practice and the SITC considers them to be “interchangeable” (8). The SmPC for cemiplimab + chemotherapy does not specify a particular PD-L1 assay.

B.2.12.2 Conclusions from the clinical evidence base

Overall, the evidence base does not suggest differences in clinical efficacy between cemiplimab + chemotherapy and pembrolizumab + chemotherapy.

In the MHRA-label population (PD-L1 ≥1%, any histology) of EMPOWER Lung-3, patients treated with cemiplimab + chemotherapy had clinically meaningful improvements in OS and PFS compared with those who received placebo + chemotherapy. There were also notable improvements in ORR and duration of response among patients treated with cemiplimab+ chemotherapy compared with those treated with placebo + chemotherapy.

As expected, the NMA used to indirectly estimate comparative efficacy and safety has limitations, due to inherent limitations in the evidence base (e.g. few trials, heterogeneity) and a lack of published data for the relevant comparator, and the results are associated with uncertainty, as reflected in the wide credible intervals around point estimates. Nonetheless, the collective indirect evidence indicates there are no clinically meaningful differences in efficacy and safety outcomes. This is the consistent view of UK clinical experts with experience of use of IO in NSCLC, and the view of other HTA bodies (CADTH, PBAC) that evaluate cost-effectiveness and have recommended cemiplimab + chemotherapy as an option in this population on the basis that it does not result in additional treatment costs vs pembrolizumab + chemotherapy (80, 81).

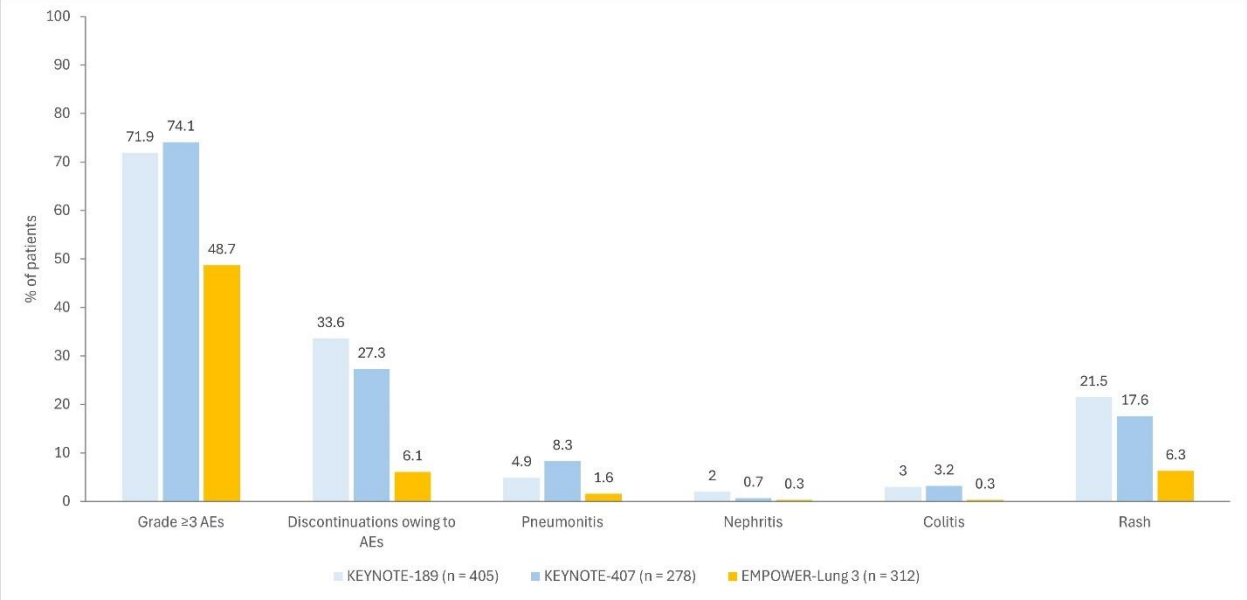
In expectation that the Blueteq protocol (i.e. NHS commissioning policy) for cemiplimab + chemotherapy would be aligned with EMPOWER-Lung 3, routine availability of cemiplimab + chemotherapy would give clinicians greater flexibility to tailor chemotherapy to individual patient characteristics, needs, and preferences. This flexibility may benefit, for example, older patients, those with renal, cardiac or hepatic impairment, or those with a high comorbidity burden.

The safety profile for cemiplimab + chemotherapy was generally similar to that previously reported for other IO + chemotherapy regimens (16, 84, 85), and was considered by the EMA to be acceptable considering the treated and targeted disease of advanced lung cancer (58).

Whilst it is not possible to draw any definitive conclusions from cross-trial comparisons, it is interesting to note that the rates of Grade ≥3 AEs, discontinuations due to AEs and

certain immune-mediated AEs were low in EMPOWER-Lung 3 in the context of results previously reported for other IO + chemotherapy regimens (Figure 13). Immune-related AEs are a consequence of non-specific activation of the immune system and immune-mediated damage; they most commonly affect the skin, endocrine system, gastrointestinal tract and liver (89). They are associated with high hospitalization rates and require prompt management to avoid severe and sometimes fatal outcomes (89). Pneumonitis is a particular concern for clinicians as it is potentially life-threatening and can lead to worse survival outcomes in patients with advanced NSCLC who receive IO + chemotherapy (90). Nephritis is important in an older patient population who may already have age-related declines in kidney function (91). Immune-related colitis has also been associated with significant morbidity (92).

Figure 13 Incidence of selected TEAEs with cemiplimab + chemotherapy (EMPOWER-Lung 3) and pembrolizumab + chemotherapy (KEYNOTE-189 and KEYNOTE-407)



Based on 2-year data from each study. Sponsor-identified immune-related AEs are reported for EMPOWER-Lung 3 and KEYNOTE-189; KEYNOTE-407 publication does not specify whether data are sponsor-identified or investigator assessed.

TEAEs, treatment-emergent adverse events

Source: Makharadze et al, 2023 (61); Gadgeel et al, 2020 (93); Paz-Ares et al, 2020 (94)

B.3 Cost-effectiveness

Note: Results below reflect the existing cemiplimab net UK price subject to the simple PAS discount already agreed with NHS England alongside TA802 (2022) for patients with advanced cutaneous squamous cell carcinoma. This is because Regeneron is currently in the process of entering negotiations with NHS England regarding commercial flexibilities to allow Regeneron to offer a cost effective price in NSCLC; therefore, this price will be updated in due course.

A key challenge associated with conducting a cost-utility analysis to address the relevant decision problem on the cost-effectiveness of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy is the lack of head-to-head RCT evidence. The NMA used to indirectly estimate comparative efficacy and safety is inherent limitations in the publicly available evidence base for the relevant comparator, including a low number of studies to inform evidence networks, and significant heterogeneity observed between studies (in terms of trial inclusion criteria, patient characteristics, and study design) as described in further detail in Section B.2.9.

While effectiveness (OS, PFS, ORR) results from the NMA suggest comparable outcomes with no statistically significant differences, the consistently wide, overlapping credible intervals, and the broader limitations of the NMA may preclude definitive conclusions about the relative efficacy of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy.

All this considered, Regeneron believes that currently, the justification for modelling equivalent efficacy for cemiplimab + chemotherapy and pembrolizumab + chemotherapy is stronger than the justification for modelling any differences in efficacy:

- The mechanism of action of cemiplimab and pembrolizumab is the same; cemiplimab and pembrolizumab, both bind to the PD-1 receptor and block its interaction with PD-L1 and PD-L2.

- The SLR did not identify any evidence showing that PFS or OS for cemiplimab and pembrolizumab, either as monotherapies or in combination with chemotherapy, are statistically significantly different.

- Cemiplimab + chemotherapy is the only IO + chemotherapy combination other than pembrolizumab + chemotherapy that has a 'preferred' NCCN guidelines recommendation for the treatment of patients with advanced/metastatic NSCLC (49). NCCN has also assigned both options with a score of 4 out of 5 ('very effective') for efficacy across histology and PD-L1 expression level subgroups in its Evidence Blocks™ assessment, which is based on both published trial evidence and real-world clinical experience of the panel members in more diverse real-world settings.

- NICE has previously noted the lack of statistically significant difference in efficacy based on NMA comparisons between other IOs in advanced/metastatic NSCLC and has consequently considered cost comparison analysis informative for decision making (e.g., atezolizumab vs pembrolizumab; TA705 FAD) (40).

- Other international HTA bodies that evaluate cost-effectiveness, including CADTH and PBAC have acknowledged limitations of the evidence base and NMA approach, and ultimately considered economic analyses assuming equivalent efficacy for cemiplimab + chemotherapy and IO + chemotherapy comparators (e.g., pembrolizumab + chemotherapy) to be a more relevant basis for decision making (80, 81).

- UK clinical expert lung oncologists noted similarity between the efficacy of cemiplimab + chemotherapy and pembrolizumab + chemotherapy and concurred that effectiveness was likely to be similar in clinical practice.

Therefore, a cost comparison analysis is included as an ‘alternative base case’ with the results presented in Section B.3.7.2.

B.3.1 Published cost-effectiveness studies

An SLR was conducted in accordance with the NICE methods guidance to identify published economic models/ evaluations, cost and resource use data, as well as any relevant utility data for patients with previously untreated advanced/metastatic NSCLC .

The original SLR was conducted in January 2020 with a global geographical scope, and a search cut-off date of 2009. Subsequent updates were conducted in January 2021 and May 2022. A UK-only update was conducted in May 2024, and all results presented in this submission were restricted to studies with a UK patient population. Results of the SLR are presented in Table 23 below.

A total of 19 economic evaluation studies with UK relevant data were identified as part of the SLR and subsequent updates, including 9 previous NICE technology appraisals. Full details of the SLR including search strategy and study selection are provided in Appendix G.

Due to an absence of studies considering the cost-effectiveness of cemiplimab _ chemotherapy vs. pembrolizumab + chemotherapy in the target population, a *de novo* model was developed. Section B.3.2.1 describes the model structure used in the analysis and Section B.3.2.2 details the rationale behind the model structure and how the data identified in the SLR informed these decisions.

Table 23 Summary of relevant cost-effectiveness studies

Study ID	Summary of model	Intervention/ comparator	Patient group (subgroup/strata)	QALYs[a]	Costs	ICER (per QALY gained) [c]
NICE submissions						
NICE TA911 (2023) (95)	Partitioned survival model; NHS and PSS perspective; Lifetime horizon of 25 years	Intervention: Selpercatinib Comparator: Pembrolizumab plus pemetrexed plus platinum containing chemotherapy; Pemetrexed plus platinum containing chemotherapy	People with advanced rearranged during transfection (RET) fusion-positive, non-small cell lung cancer (NSCLC) who require systemic therapy	NR	NR	Selpercatinib versus pemetrexed plus platinum chemotherapy arm: £35,883/QALY Selpercatinib versus Pembrolizumab combination arm: £5,264/QALY
NICE TA812 (2022) (95)	Partitioned survival model; NHS and PSS perspective; Lifetime horizon of 25 years	Intervention: Pralsetinib Comparator: Platinum based chemotherapy with or without pemetrexed; Pembrolizumab combination with Pemetrexed plus Chemotherapy	Adult patients with RET fusion-positive advanced NSCLC not previously treated with a RET inhibitor.	NR	NR	NR
NICE TA770* (2022) (38)	Partitioned survival model; UK NHS perspective; Lifetime horizon of 30 years	Intervention: KEYNOTE 407; Pembrolizumab, KEYNOTE 042; Pembrolizumab Comparator: KEYNOTE 407; Chemotherapy, KEYNOTE 042; Chemotherapy	Adults with untreated, metastatic, squamous non-small-cell lung cancer	NR	NR	Pembrolizumab arm: £38,090/QALY
NICE TA724 (2021) (96)	Partitioned survival model, NHS and personal social services perspective, 25 years	Intervention Nivolumab + ipilimumab + chemotherapy	Previously untreated patients with stage IV or recurrent NSCLC harboring no EGFR or ALK aberrations	NR	NR	**Nivolumab + ipilimumab vs:** Chemotherapy £29,139 Pembrolizumab

		Comparator Chemotherapy Pembrolizumab Atezolizumab + bevacizumab + paclitaxel + carboplatin				Dominant Atezolizumab + bevacizumab + carboplatin + paclitaxel Dominant
NICE TA705 (2021) (40)	Partitioned survival model, NHS and personal and social services, 20 years lifetime	Intervention Atezolizumab Comparator Pembrolizumab	Previously untreated patients with advanced NSCLC of any histology without EGFR mutations or ALK alterations with PD-L1 score of TC3 (PD-L1 expression on ≥50% of tumour cells) or IC3 (PD-L1-expressing immune cells being ≥10% of the tumour area) as measured by the SP142 PD-L1	0.08 incremental	£47,059 incremental	£56,0832
NICE TA600 (2019) (97)	Partitioned survival model NHS and Personal and Social Services perspective Lifetime horizon (30 years)	Intervention Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel Comparator carboplatin + paclitaxel/nab-paclitaxel platinum + paclitaxel platinum + docetaxel platinum + gemcitabine	Previously untreated patients with metastatic squamous NSCLC of varying PD-L1 expression levels	**Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel** vs : carboplatin + paclitaxel/nab-paclitaxel 1.68 incremental platinum + paclitaxel 1.68 incremental platinum + docetaxel 1.78 incremental platinum + gemcitabine 0.66 incremental	Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel £72,695 carboplatin + paclitaxel/nab-paclitaxel £24,417 platinum + paclitaxel £22,002 platinum + docetaxel £21,184 platinum + gemcitabine £30,947	Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs carboplatin + paclitaxel/nab-paclitaxel £28,672 Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs platinum + paclitaxel £30,156 Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel vs platinum + docetaxel £28,927 Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel

						vs platinum + gemcitabine £63,661
NICE TA584 (2019) (43)	Partitioned survival model, NHS and personal and social services, 20 years lifetime	Intervention Atezolizumab + carboplatin + paclitaxel + bevacizumab Comparator Chemotherapy (pemetrexed + platinum)	Previously untreated patients with metastatic non-squamous NSCLC with low or negative PD-L1 expression (TPS 0–49%, TC/IC 0,1,2)	Atezolizumab + carboplatin + paclitaxel + bevacizumab 1.5 Chemotherapy (pemetrexed + platinum) 1.01 Atezolizumab + carboplatin + paclitaxel + bevacizumab 1.68 Pemetrexed + platinum + pemetrexed maintenance 1.39	NR	NR
NICE TA557 (2019) (98)	Partitioned survival model, NHS and personal and social services perspective, lifetime 20 years	Intervention Pembrolizumab + chemotherapy (pemetrexed + cisplatin/carboplatin) Comparator Platinum based chemotherapy (pemetrexed + cisplatin/carboplatin) Platinum based chemotherapy (platinum + paclitaxel) Platinum based chemotherapy (platinum + docetaxel) Platinum based chemotherapy (platinum + gemcitabine)	Previously untreated patients with non-squamous metastatic (stage 4) NSCLC tumor(s) without sensitizing mutations of EGFR or ALK translocations	**Pembrolizumab + chemotherapy (pemetrexed + cisplatin/carboplatin)** vs: platinum based chemotherapy (pemetrexed + cisplatin/carboplatin) 0.89 vs platinum + paclitaxel 1.08 vs platinum + docetaxel 0.73 vs platinum + gemcitabine 1.01 vs platinum + vinorelbine 0.9 Vs platinum + pemetrexed 0.9	Platinum based chemotherapy (pemetrexed + cisplatin/carboplatin) £42,980 pembrolizumab + chemotherapy (pemetrexed + cisplatin/carboplatin) £84,324 platinum + paclitaxel £25,368 platinum + docetaxel £27,391 platinum + gemcitabine £26,572 platinum + vinorelbine £27,663 platinum + pemetrexed £42,247	**Pembrolizumab + chemotherapy (pemetrexed + cisplatin/carboplatin)** vs: platinum based chemotherapy (pemetrexed + cisplatin/carboplatin) £46,568 vs platinum + paclitaxel £15,4654 vs platinum + docetaxel £78,242 vs platinum + gemcitabine £57,064 vs platinum + vinorelbine £63,262 Vs platinum + pemetrexed £46,504

		Platinum based chemotherapy (platinum + vinorelbine) Platinum based chemotherapy (platinum + pemetrexed)				
NICE TA531 (2018) (39)	Partitioned survival model, NHS Personal and Social services perspective, lifetime 20 years	Intervention Pembrolizumab Comparator Chemotherapy	Previously untreated metastatic non-small-cell lung cancer (NSCLC) with a PD-L1 tumor proportion score (TPS) ≥ 50% and no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase genomic tumor aberrations	0.96 incremental	NR	NR
SMC submissions						
SMC2573 (2023) (99)	Partitioned survival model; NHS Scotland and social care perspective; Lifetime horizon of 25 years	Intervention: Selpercatinib Comparator: Pembrolizumab plus Pemetrexed plus platinum containing chemotherapy; Pemetrexed plus platinum containing chemotherapy	Adults with advanced RET fusion-positive NSCLC who have not been previously treated with a RET inhibitor and are treatment-naïve.	NR	NR	Selpercatinib versus pemetrexed plus platinum chemotherapy arm: £35,883/QALY Selpercatinib versus Pembrolizumab combination arm: £5,264/QALY
SMC2496 (2023) (100)	Partitioned survival model; Lifetime horizon of 25 years	Intervention: Pralsetinib Comparator: Platinum based chemotherapy with or without pemetrexed and Pembrolizumab combination with Pemetrexed plus Chemotherapy	Aged ≥18 years with unresectable, locally advanced or metastatic solid tumours, and a pathologically or genetically documented RET fusion or mutation. Patients had an ECOG-PS score of 0 to 2.	Pralsetinib arm: 3.11 Pembrolizumab plus pemetrexed plus chemotherapy arm: 1.3	Pralsetinib arm: £155,912 Pembrolizumab plus pemetrexed plus chemotherapy arm: £109,775	Pralsetinib arm: £25,371/QALY
SMC 2397 (2022) (101)	Partitioned survival model, public	Intervention Nivolumab + ipilimumab + chemotherapy	Previously untreated patients with metastatic NSCLC harboring no EGFR or ALK	NR	NR	**Squamous** nivolumab + ipilimumab + chemotherapy

	perspective, 25 year time horizon	<u>Comparator</u> Chemotherapy Pembrolizumab + chemotherapy	aberrations with PD-L1 <50%			vs chemotherapy £96,922 vs pembrolizumab + chemotherapy Extendedly dominated **Non-squamous** nivolumab + ipilimumab + chemotherapy vs chemotherapy £82,130 vs pembrolizumab + chemotherapy Dominated
SMC 2379 (2021) (102)	Partitioned survival model, public perspective, 20 year time horizon	<u>Intervention</u> Atezolizumab <u>Comparator</u> Pembrolizumab	Previously untreated patients with 1L metastatic NSCLC harbouring no EGFR or ALK aberrations and PD-L1 TC3/IC3	NR	NR	£58,0523
SMC1239/17 (2017) (103)	Partitioned survival model, public perspective, 20-year time horizon	<u>Intervention</u> Pembrolizumab <u>Comparator</u> Chemotherapy	Previously untreated metastatic non-small-cell lung cancer (NSCLC) with a PD-L1 tumor proportion score (TPS) ≥ 50% and no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase genomic tumor aberrations	NR	NR	£41,213
Studies in the literature						
Jiang (2023) (104)	Partitioned survival model; UK healthcare system perspective; Lifetime horizon of 10 years	<u>Intervention:</u> Atezolizumab <u>Comparator:</u> Chemotherapy (vinorelbine or gemcitabine)	Patients with stage IIIB or stage IV NSCLC, who were ineligible for platinum-based therapy, had an ECOG PS of 2–3, and possessed wild-type EGFR or ALK gene mutations	Atezolizumab arm: OS group: 0.86 PFS group: 0.38 Chemotherapy arm: OS group: 0.58 PFS group: 0.24	Atezolizumab arm: £56,949.71 Chemotherapy arm: £30,743.67	OS group: £94,873/QALY PFS group: £213,196/QALY
Verma (2020) (105)	Partitioned survival model, UK healthcare perspective, 20 year time horizon	<u>Intervention</u> Pembrolizumab <u>Comparator</u>	Previously untreated patients with advanced or metastatic NSCLC*	0.05 incremental	£7,182 incremental	£154,805

		Nivolumab	*PD-L1 expression data not reported, although KEYNOTE-024 encompassed patients with PD-L1 >=50%			
Hu (a) (2018) (106)	Markov model, UK health care perspective, time horizon – until 99% patients died, lifetime assumed	Intervention Pembrolizumab Comparator Chemotherapy	Previously untreated metastatic non-small-cell lung cancer (NSCLC) with a PD-L1 tumor proportion score (TPS) ≥ 50% and no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase genomic tumor aberrations	0.83 incremental	Pembrolizumab £92,833 Chemotherpay £20,368	£86,913
Hu (b) (2018) (107)	Markov model, UK healthcare perspective	Intervention Pembrolizumab + chemotherapy Comparator Chemotherapy	Patients with NSCLC who are chemotherapy naïve regardless of PD-L1 tumor proportion score	pembrolizumab + platinum-based chemotherapy vs Platinum-based chemotherapy 0.62 incremental	pembrolizumab + platinum-based chemotherapy £77,355 Platinum-based chemotherapy £21,405	£89,997
Georgieva (2018) (108)	Bayesian Markov model, British NHS perspective, lifetime (20 year) time horizon	Intervention Pembrolizumab Comparator Chemotherapy	Previously untreated metastatic non-small-cell lung cancer (NSCLC) with a PD-L1 tumor proportion score (TPS) ≥ 50% and no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase genomic tumor aberrations	Chemotherapy 1.11 Pembrolizumab (with end of life adjustment 3.06 Pembrolizumab (without end of life adjustment) 1.93	Chemotherapy $34,000 Pembrolizumab $99,000	With end of life adjustment (no dependency) $34,000 Without end of life adjustment (no dependency) $81,000

[a]Data reported are in total QALYs; [b]Total cost; [c]ICERs reported for base case in intervention and comparator arms (specified). *NICE TA770 is reported separately from TA600 as it was a reappraised as part of the Cancer Drugs Fund. However, while the amount of information differed between the submissions they are based on the same dossier,
ALK, anaplastic lymphoma kinase; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; EGFR, epidermal growth factor receptor; ICER, Incremental Cost-Effectiveness Ratio; NHS, National Health Service; NR, Not Reported; NSCLC, non-small cell lung cancer; QALY, Quality Adjusted Life Years; RET, REarranged during Transfection; UK, United Kingdom .

B.3.2 Economic analysis

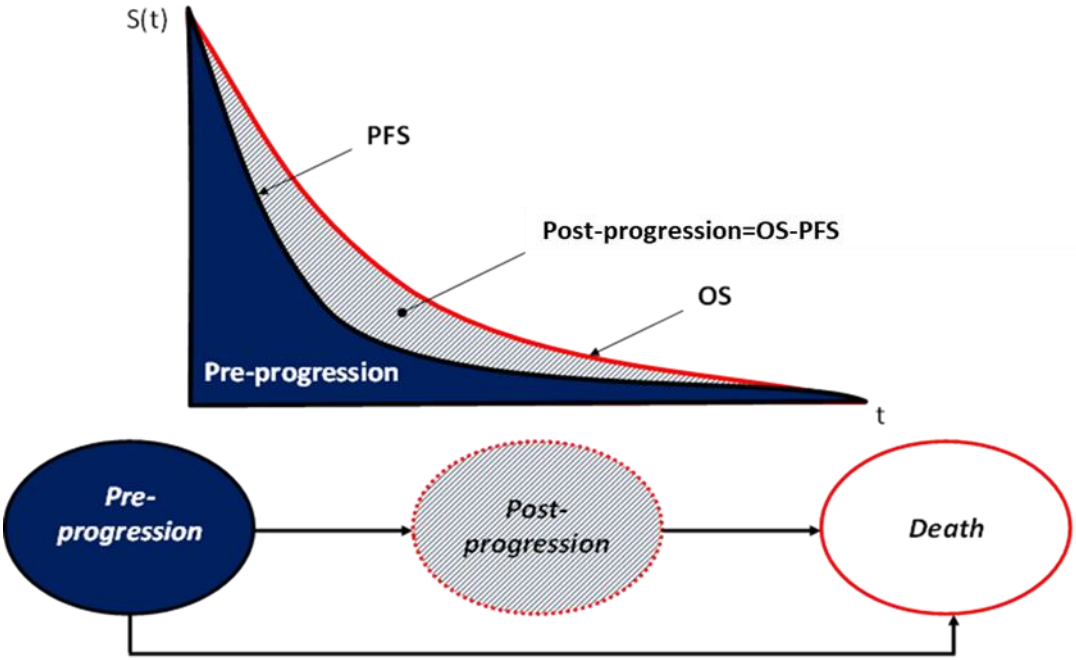
B.3.2.1 Model structure

The model aimed to evaluate the cost-effectiveness of cemiplimab plus platinum-based chemotherapy as a first-line treatment for adult patients with untreated locally advanced, who are not a candidate for definitive chemoradiation, or metastatic NSCLC which expresses PD-L1 on 1% or more of tumour cells and has no EGFR, ALK or ROS-1 genetic alterations.

The evaluation was conducted from a United Kingdom (England) healthcare payer perspective.

This cost-effectiveness model was based on a 'time-in-state' structure (otherwise known as a 'partitioned survival model' or 'area under the curve' [AUC] model). A schematic of the model structure is presented in Figure 14. Patients begin in the pre-progression health state where they receive either therapy or a relevant comparator treatment (e.g., pembrolizumab + chemotherapy) and are progression-free. Over time, patients transition directly to the death state, or to the post-progression health state where patients receive subsequent treatments before moving to the death state. Further details of subsequent treatments are provided in Section B.3.5.3. This model structure aligns with the accepted approach taken by the majority of prior NSCLC TAs, as outlined in Section B.3.1.

Figure 14 Overview of model structure



Model uses monthly cycles; Abbreviations: PFS, progression-free survival; OS, overall survival

The proportion of patients in the pre-progression health state reduces over time according to the treatment-specific (either constant or time-varying) hazard rates at which patients leave this state, which corresponds to PFS. The proportion of patients who have died increases over time according to (either constant or time-varying) treatment-specific death rates corresponding to OS. The difference between the proportion of patients alive and proportion of patients in the pre-progression health state represents the proportion of patients in the post-progression health state at any point in time.

The model was programmed in Microsoft Excel 365 (v16.0), with Visual Basic for Applications (VBA) used to automate sensitivity analyses, facilitate model selections, and navigation.

Key features of the economic analysis are described in Table 24.

Table 24 Features of the economic analysis

Factor	Chosen values	Justification
Time horizon	30 years	Considered to be appropriate as the lifetime of patients with advanced or metastatic NSCLC considering baseline median age of target population (PD-L1 ≥1%, any histology) in EMPOWER-Lung 3 was 62 years old.
Cycle length	One month	Considered appropriate given dosing frequency, frequency of trial outcomes collection and time horizon of model.
Half cycle correction	Yes	Considered appropriate given monthly cycle length.
Discount of 3.5% for utilities and costs	Yes	Consistent with the NICE reference case (109).
Were health effects measured in QALYs? If not, what was used?	Yes	Consistent with the NICE reference case (109).
Source of efficacy	EMPOWER-Lung 3 (reference arm) and network meta-analysis for the PD-L1 ≥1%, any histology population.	Consistent with the cemiplimab MHRA marketing authorisation and NICE reference case.(109). Best use of available data to inform indirect comparisons; efficacy outcomes (e.g., PFS/OS) are expected to be broadly similar irrespective of histology or PD-L1 level based on feedback from UK clinical expert lung oncologists. The use of an alternative reference arm source is explored as a scenario.
Source of safety	ITT population (i.e., 'any PD-L1' population)	Maximizes use of available safety data from EMPOWER-3; safety outcomes are not anticipated to be meaningfully impacted by PD-L1 level based on feedback from UK clinical expert lung oncologists.
Source of utilities	EORTC-QLQ C30 collected in EMPOWER-Lung 3 mapped to the EQ-5D-3L (UK tariff)	Consistent with the NICE reference case (109). Alternative sources of HSUV are explored as a scenario.
Source of costs	Published literature, resource utilisation, and costs accepted in previous NICE submissions.	These reflect resource utilisation and costs accepted in previous NICE submissions (TA531, TA347, TA428) (35, 39, 46).
Treatment waning effect?	Yes, from five years the hazards for cemiplimab + chemotherapy and pembrolizumab + chemotherapy are assumed equal to chemotherapy for PFS and OS.	There is now long-term evidence of a robust and durable treatment effect lasting beyond discontinuation for IOs, and treatment effects up to five years have been accepted for other IO combinations in this disease area (38, 44). UK clinical expert lung oncologists confirmed that long-term follow-up data for pembrolizumab + chemotherapy is appropriate to inform modelling assumptions about efficacy of cemiplimab + chemotherapy beyond the 2-year follow-up for EMPOWER-Lung 3 reported to date. Alternative assumptions around duration of effect are explored in scenarios.

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, HSUV, health state utility values, ITT, Intention to treat, IOs, immunotherapies, NICE, National Institute for Health and Care Excellence; NSCLC,

non-small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QALY, quality-adjusted life year; TA, technology appraisal, UK, United Kingdom

B.3.2.2 Model structure rationale

Based on the data available to inform this analysis, the partitioned survival model structure was considered the most appropriate model structure, being more likely to result in a credible representation and extrapolation of the clinical outcomes than alternative methodologies, while requiring fewer assumptions in the absence of complete clinical data (reasons as summarised in Table 25). Partitioned survival model structures are a well-established approach to modelling NSCLC treatments in prior NICE TAs and a total of 16 economic evaluations identified in the SLR detailed in section B.3.1 used a partitioned survival model structure.

Table 25 Key strengths of partitioned survival model structure for cost-effectiveness model

Strengths	Application in analysis
Can be implemented using IPD or summary data	• The PSM has the flexibility to incorporate IPD from the EMPOWER-Lung 3 phase 3 trial and aggregate data from comparator trials.
Can use OS and PFS directly from clinical trial to inform health-state occupancy with appropriate dependencies	• As described by the NICE DSU TSD 19,(110) a key advantage of the PSM approach is that it aligns with the endpoints as observed in clinical studies and allows the time-dependency in the risk of events over time to be captured since survival is modelled as a function of time since model entry, implying a close fit to the actual PFS and OS data (i.e., KM curves) as observed in the clinical studies for the relevant interventions. • The OS and PFS of cemiplimab + chemotherapy and chemotherapy were analysed under the survival framework and were used directly as inputs in a PSM structure, making the model intuitive and straightforward to communicate.
Treatment effects derived from NMA can easily be incorporated by applying HRs to the OS and PFS of the reference curve	• The outputs of the NMA from phase 3 trials were directly usable as inputs in a PSM structure requiring no additional assumptions to incorporate in the cost-effectiveness analysis.
Avoid assumptions for transitional probabilities required by Markov models when IPD are not available	• Although it is possible to build time-dependent probabilities into a Markov model (i.e., semi-Markov models through the use of tunnel states), to do so requires assumptions when IPD are not available for all studies. • For this analysis, studies assessing relevant comparators beyond EMPOWER-Lung 3 did not report data on the probability of death without progression, and as a result, to employ a Markov structure assumption would be required regarding how patients transition between these states beyond the observed data. This would challenge the underlying foundations of the model and thus, further supports the use of the time-in-state approach.

DSU, Decision Support Unit; HRs, hazard ratios, IPD, individual patient-level data; KM, Kaplan Meier; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; TSD; technical support document.

The NICE DSU highlighted several potential issues that can be encountered with time-in-state models and have made recommendations on how such models should be reported so that the impact of these can be adequately assessed (111). These recommendations, along with how they were accounted for in this analysis, are summarised in Table 26.

Table 26 Decision support unit recommendations for time-in-state models and applications for the proposed analyses

DSU recommendation	Application in analysis
Report model conceptualisation with rationale for the 'Partitioned survival analysis'	• Rationale based on population of interest, natural history of disease, and data availability. See Section B.3.2.3 for further details.
Summarize key assumptions	• PFS and OS are modelled and extrapolated independently even though these two endpoints are inherently linked • Trends in the hazard rate of PFS and OS within the trial period are assumed to be generalisable to the extrapolation period, with the impact of these assumptions explored through a series of sensitivity analyses
Recognize limitations for extrapolation	• Challenge to explore the relationship between treatment effect pre-& post-progression
Consider all relevant evidence for extrapolation	• Validation with real-world evidence and more mature data from external sources (other trials for IOs) • Expert involvement – long-term survival was validated by UK clinical expert lung oncologists (see Section B.3.8.5)
Present within-trial survival curves for individual clinical events	• Within trial survival curves from EMPOWER-Lung 3 are included to validate extrapolations
Present alternative assumptions regarding extrapolation	• Continuation of treatment effect (called "Extrapolation of HR trend" in the model): Continuation of hazards based on observed effects in trial over the duration of the model time horizon. • Treatment waning effect: Continuation of hazards based on observed effects in trial for specific period (i.e., up to 108 weeks), then equal to or waning to hazards of a comparator. • Last HR carried forward: Time-varying hazard ratios to be held constant beyond a user-defined time point.

DSU, Decision Support Unit; IOs, immunotherapies; KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival.

B.3.2.3 Patient population

The patient population included in the economic evaluation consisted of adult patients with locally advanced or metastatic, squamous or non-squamous NSCLC who were previously untreated with systemic therapy for their advanced or metastatic disease with PD-L1 ≥1%, and no EGFR, ALK or ROS1 aberrations. This population aligns with the MHRA label population and the overall NICE scope of this submission.

The characteristics of the model cohort align with the PD-L1 ≥1%, any histology subgroup of EMPOWER-Lung 3. Table 27 presents key baseline characteristics used within the economic model, which are consistent with the broader set of characteristics previously presented in Table 6. The patient characteristics of the EMPOWER-Lung 3 trial were considered generalisable to UK clinical practice by UK clinical expert lung oncologists interviewed as part of the model validation process.

Several subgroups based on histology and PD-L1 expression level that align with decision nodes in current NICE guidelines for NSCLC (112), were included in the analysis and comprise:

- Squamous, PD-L1 1-49%
- Squamous, PD-L1 ≥50%
- Non-squamous, PD-L1 1-49%
- Non-squamous, PD-L1 ≥50%

Patient characteristics for subgroup analyses are available in Table 91 and Table 92 and the survival analysis methods for these subgroups are detailed in Appendix Q. While the cost-effectiveness analysis includes these subgroups in recognition of the NICE scope, we consider the PD-L1 ≥ 1% overall population to be the relevant population for decision making as (1) pembrolizumab + chemotherapy remains the key comparator within these subgroups (2) there is no evidence to suggest that clinical effectiveness differs within these subgroups (see Appendix E), an assumption confirmed by UK clinical expert lung oncologists and (3) cost-effectiveness does not differ between these subgroups (see Section B.3.8.4).

While the NICE scope also included subgroup analyses by cancer stage (locally advanced vs. metastatic), UK clinical expert lung oncologists did not consider that clinical effectiveness or costs would differ, therefore no cost-effectiveness analysis is presented by cancer stage. Similarly, newly diagnosed vs. recurrent after surgery metastatic disease was not consider a relevant subgroup for consideration by UK clinical expert lung oncologists.

Table 27 Patient characteristics included in the model, EMPOWER-Lung 3 June 2022 PD-L1 ≥1% any histology

Characteristic	Total, PD-L1 ≥1% any histology (N=327)
Median age, years (range)	62 (25-84)
Sex, female (%)	54 (16.5)
Mean weight, kg (sd)	72.79 (15.63)
Mean BSA, (sd)	1.834 (0.2)

BSA, body surface area; PD-L1, programmed death ligand 1; sd, standard deviation.

B.3.2.4 Intervention technology and comparators

In alignment with the decision problem outlined in Section B.1.1, the current analysis investigates the cost-effectiveness of cemiplimab + chemotherapy compared to pembrolizumab and chemotherapy for the treatment of untreated advanced or metastatic NSCLC with PD-L1 ≥1%.

The analysis considers pembrolizumab and chemotherapy to be the only relevant comparator population. Firstly, patients treated with combination therapy form a clinically distinct group from those treated with chemotherapy alone or IO alone, as discussed in detail in Section B.1.1, therefore chemotherapy alone or IO monotherapy are not considered relevant comparators. Secondly, pembrolizumab has a >80% market share among NICE-recommended IO + chemotherapy options across histologies and PD-L1 expression levels ≥1% (2) and is the only IO + chemotherapy option whose includes the entirety of the population within the scope, therefore other IO + chemotherapy combinations were not considered relevant comparators.

As outlined in Section B.1.1, four subgroups were considered in the analysis based on histology and PD-L1 status. The two squamous subgroups were compared against pembrolizumab with carboplatin and paclitaxel while the non-squamous subgroups were compared to pembrolizumab with pemetrexed and platinum chemotherapy. These differences in chemotherapy regimens were chosen to reflect current clinical practice and align with the NICE NSCLC clinical guidelines which also segment patients by histology and PD-L1 status (112).

Details on the dosing regimens for both cemiplimab and pembrolizumab used in the base-case analysis are given in Section B.3.5.2. Although the chemotherapy backbone used in the KEYNOTE studies was slightly different from that used in the EMPOWER-Lung 3 study, feedback from UK clinical expert lung oncologists was that the efficacy of the different chemotherapy regimens used for pembrolizumab and cemiplimab were broadly similar. Therefore, for simplicity and to avoid any bias in costs in the model from different chemotherapy backbones, the chemotherapy distribution for all arms in the model was based on the observed distribution of chemotherapies from the pooled arms of the EMPOWER-Lung 3 study. Note that this assumption affects only the drug acquisition and administration costs in the model (see Section B.3.5.1 for further details).

B.3.3 Clinical parameters and variables

B.3.3.1 Method of modelling progression-free and overall survival

In the absence of a head-to-head RCT, the following sections use evidence from the NMA described in Section B.2.9 to derive estimates of relative treatment effects between cemiplimab + chemotherapy versus pembrolizumab + chemotherapy for the cost-utility model.

B.3.3.1.1 Model selection: reference arm

To include the NMA in the CEM, the relative treatment effects from the NMA are anchored onto estimates of absolute PFS and OS (i.e., the reference arm).

As discussed in Section B.3.2.3, the EMPOWER-Lung 3 trial was considered broadly generalisable to UK clinical practice. The patients recruited to EMPOWER-Lung 3 were aligned with the population in the NICE scope, whereas patients in the KEYNOTE studies included any level of PD-L1 expression, were all Stage IV (compared to 85% Stage IV in the EMPOWER-Lung 3 ITT cohort) and had better Eastern Cooperative Oncology Group performance status (ECOG-PS of 0 of ~37% across pooled KEYNOTE studies compared to 15% in the EMPOWER-Lung 3 ITT cohort). The chemotherapy arm of EMPOWER-Lung 3 was therefore used as the reference arm in the model. A

further advantage to anchoring the relative treatment effects to the chemotherapy arm from EMPOWER-Lung 3 is that the estimated PFS and OS for cemiplimab + chemotherapy should align with the cemiplimab + chemotherapy Kaplan-Meiers (KMs) from the EMPOWER-Lung 3 trial, allowing for assessment of internal validity of the relative treatment effects from the NMA.

Although longer follow-up is available from the KEYNOTE-407 and KEYNOTE-189 studies than in EMPOWER-Lung 3, the KMs for chemotherapy across all studies were similar (see Figure 15 and Figure 16) and landmark survival estimates from the KEYNOTE-189 and 407 studies were used to validate long-term survival estimates and model selection in the current analysis.

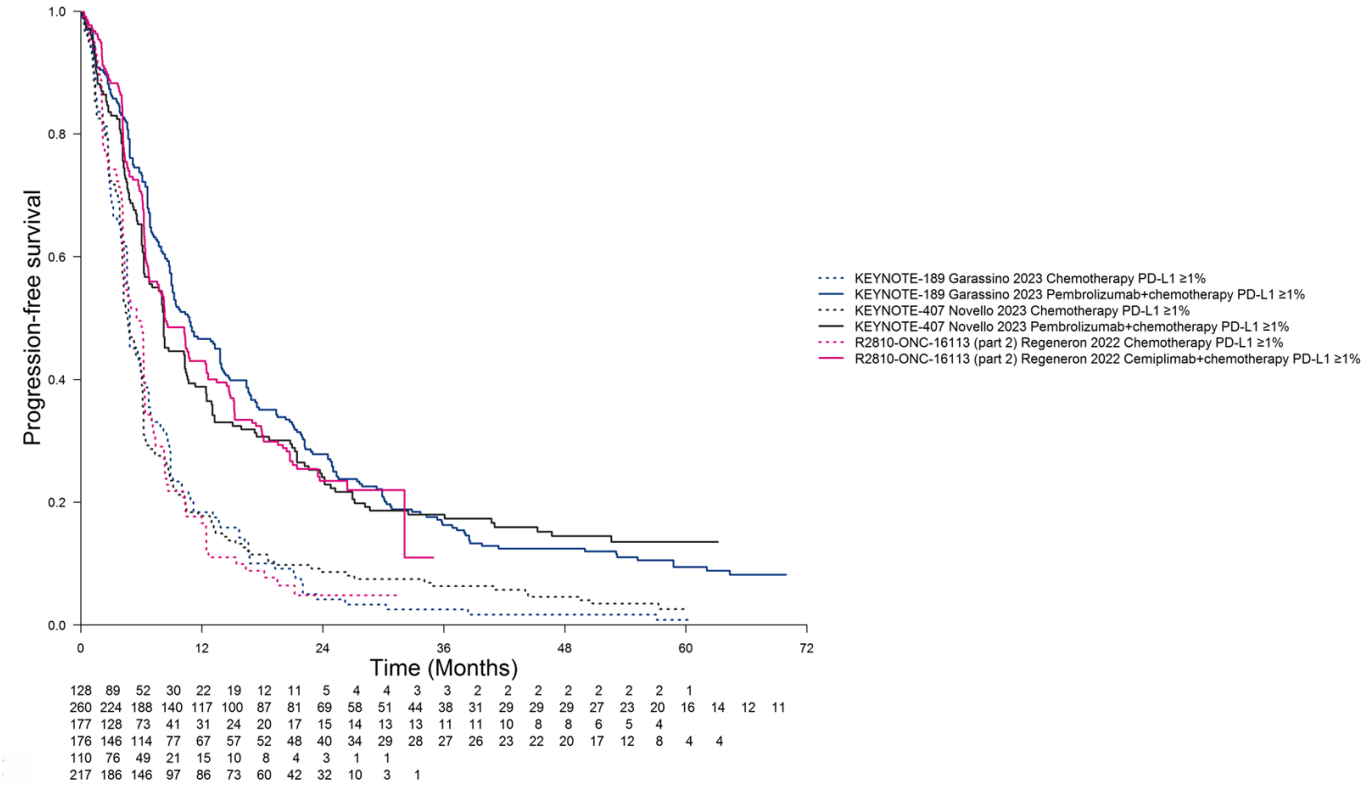
In order to investigate sensitivity of the model to the choice of reference arm, pooled KEYNOTE-189 and 407 studies are evaluated as the reference arm in a scenario analysis.

Table 28 Summary of baseline patient characteristics for any PD-L1, any histology, EMPOWER-Lung 3 vs. KEYNOTE studies

Trial	Treatment	N	Age, median	Male, n (%)	Race, n (%)		Smoking status, n (%)			ECOG performance status, n (%)		Histology, n (%)		Disease stage at baseline, n (%)			Brain mets at baseline, n (%)	Liver mets at baseline, n (%)
					East Asian	Non-East Asian	Current smoker	Former smoker	Never smoker	0	1	Sq	Non-sq	Stage IIIB	Stage IIIC	Stage IV		
EMPOWER-Lung 3	Cemi + IC chemo	312	63.0	268 (85.9)	45 (14.4)	267 (85.6)	269 (86.2)[a]		43 (13.8)	51 (16.3)	259 (83.0)	133 (42.6)	179 (57.4)	45 (14.4)		267 (85.6)	24 (7.7)	49 (15.7)
	IC chemo	154	63.0	123 (79.9)	16 (10.4)	138 (89.6)	130 (84.4)[a]		24 (15.6)	18 (11.7)	134 (87.0)	67 (43.5)	87 (56.5)	24 (15.6)		130 (84.4)	7 (4.5)	23 (14.9)
KEYNOTE weighted average by treatment arm	Pembro + chemo	--	64.8	(66.3)	(8.4)	(91.6)	(88.7)		(11.7)	(38.1)	(61.9)	(36.4)	(63.6)	--	--	(99.9)	(13.6)	(16.1)
	Chemo	--	64.2	(67.3)	(11.5)	(88.5)	(90.4)		(9.6)	(36.2)	(63.8)	(49.8)	(50.1)	--	--	(99.5)	(11.8)	(23.8)
KEYNOTE-407 (sq)	Pembro + carbo +pac/nab-pac	278	65.0	220 (79.1)	54 (19.4)	224 (80.6)	256 (92.1)[b]		22 (7.9)	72 (26.3)	205 (73.7)	272 (97.8)[c]	--	--	--	278 (100.0)[e]	20 (7.2)	--
	IC chemo	281	65.0	235 (83.6)	52 (18.5)	229 (81.5)	262 (93.2)[b]		19 (6.8)	90 (32.0)	191 (68.0)	274 (97.5)[c]	--	--	--	281 (100.0)[e]	24 (8.5)	--
KEYNOTE-021G (non-sq)	Pembro + pem + carbo	60	62.5	22 (37.0)	5 (8.0)[d]	55 (92.0)[d]	45 (75.0)[b]		15 (25.0)	24 (40.0)	35 (58.0)	--	60 (100.0)[e]	1 (2.0)	--	59 (98.0)	9 (15.0)	--
	Carbo + pem	63	63.2	26 (41.0)	5 (8.0)[d]	58 (92.0)[d]	54 (86.0)[b]		9 (14.0)	29 (46.0)	34 (54.0)	--	63 (100.0)[e]	2 (3.0)[f]	--	60 (95.0)	6 (10.0)	--
KEYNOTE-189 (non-sq)	Pembro + cis/carbo + pem	410	65.0	254 (62.0)	4 (1.0)	406 (99.0)	362 (88.3)[b]		48 (11.7)	186 (45.4)	221 (53.9)	--	410 (100.0)[e]	--	--	410 (100.0)[e]	73 (17.8)	66 (16.1)
	IC chemo	206	63.5	109 (52.9)	6 (2.9)	200 (97.1)	181 (87.9)[b]		25 (12.1)	80 (38.8)	125 (60.7)	--	206 (100.0)[e]	--	--	206 (100.0)[e]	35 (17.0)	49 (23.8)

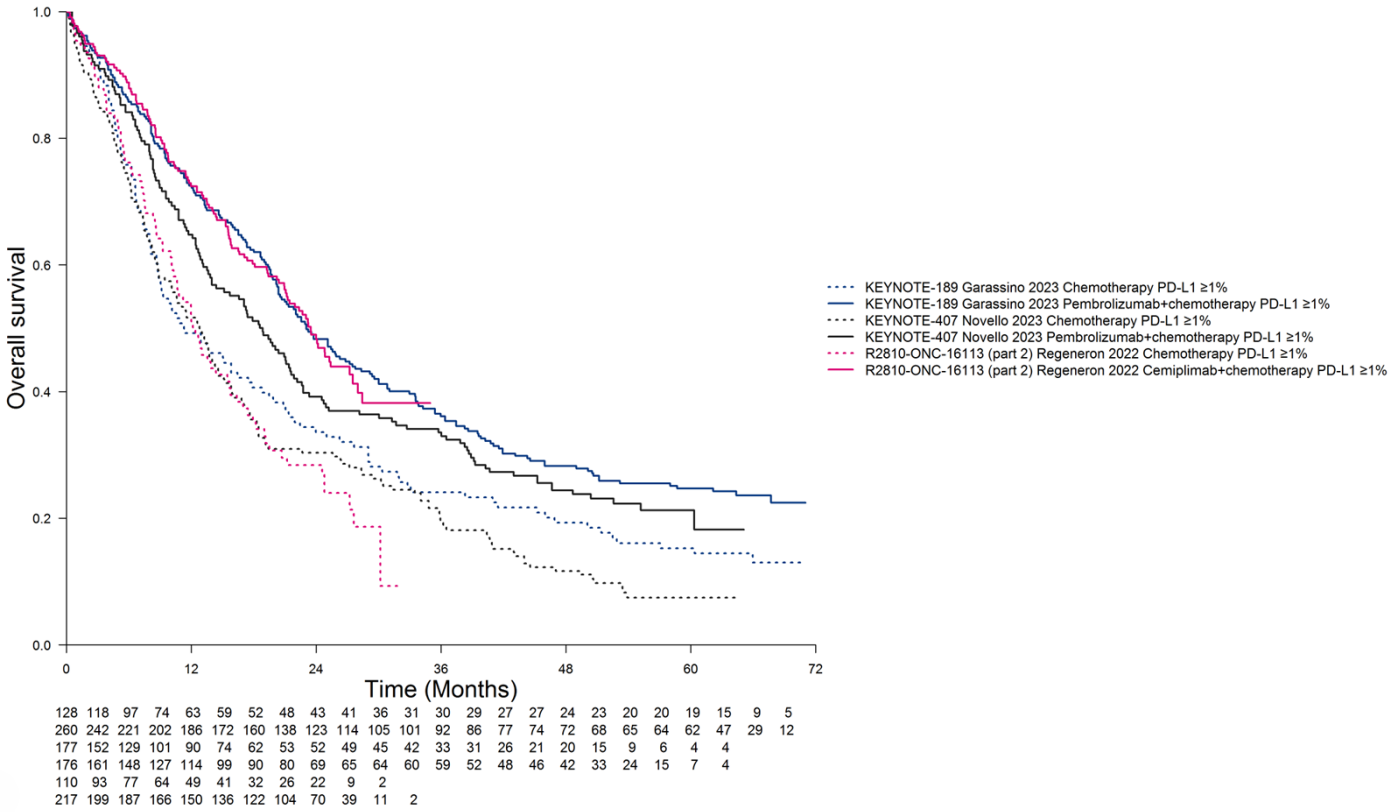
Highlighting indicates similarity (green), some differences (yellow), and major differences (red) relative to EMPOWER-Lung 3. Grey shading indicates the three trials that were used to generate the KEYNOTE weighted averages. a) Calculated as the sum of current and former smoking status; b) Reported as current/former smoking status; c) 2.2% of patients in the Pembro + IC chemo arm and 2.5% of patients in the IC chemo arm were of adenosquamous histology. Although squamous histology was a criteria for entry, patients whose tumours were of a mixed histology were eligible if there was a squamous component in the specimen; d) Patients were broadly classified based on race; e) Assumed based on trial eligibility criteria; f) One patient treated with carbo+pem had stage IIIA disease; g) Calculated. Abbreviations: Carbo, carboplatin; Cemi, cemiplimab; Chemo, platinum-based chemotherapy; ECOG, Eastern Oncology Cooperative Group; IC, investigator's choice; ITT, intention to treat; Mets, metastases; Nab-pac, nab-paclitaxel; Non-sq, Non-squamous; Pac, paclitaxel; Pem, pemetrexed; Pembro, pembrolizumab; Pop, population; Sq, squamous.

Figure 15 Progression-free survival Kaplan-Meier curves by trial for patients with PD-L1 ≥1% and any histology



PD-L1, programmed death ligand 1.

Figure 16 Overall survival Kaplan-Meier curves by trial for patients with PD-L1 ≥1% and any histology



PD-L1, programmed death ligand 1.

B.3.3.1.2 Model selection: approach to parametric fitting and assessment

The following standard parametric models were fit to the OS and PFS data for the chemotherapy reference arm to extrapolate treatment effects for cemiplimab + chemotherapy and pembrolizumab + chemotherapy over the model time horizon: exponential, Gompertz, Weibull, log-normal, log-logistic, gamma, and generalised gamma (see Section B.2.9). To align with the generalised gamma model included in the two-step NMA, the generalised gamma was restricted so that the third parameter was fixed (i.e., fixed Q, simplified to two parameter model). More flexible models were not considered given the standard parametric models generally fit the data well. Treatment-specific outcomes (i.e., PFS and OS) for all non-reference interventions (e.g., cemiplimab + chemotherapy and pembrolizumab + chemotherapy) were estimated through the application of treatment effects from the two-step multivariate NMA to the shape and scale parameters for the reference curve, or the application of a constant HR

in scenario analyses. Note that when applying time-varying HRs from the two-step multivariate NMA, the standard parametric distribution used for the reference arm and that from the two-step NMA should align. That is, if the selected NMA parametric distribution was lognormal then the reference survival curve should also be a lognormal distribution.

To select the appropriate PFS and OS reference curves, a combination of the below technical and clinical validation criteria was used. For the base case “PD-L1 ≥1%, any histology” (MHRA label) population, the reference curve selection process is described in Section B.3.3.2.

Technical validation criteria:

- **Statistical goodness of fit:** For the reference curve, the fit of the competing statistical models to the data were compared based on Akaike’s information criterion (AIC) and Bayesian information criterion (BIC), with lower values indicative of better statistical fit. Evaluation of AIC was based on Burnham and Anderson (2004) (113) where models within four points of the lowest AIC were considered reasonable fits (i.e. substantial/reasonable support or evidence of similar fit). Evaluation of the BIC was based on the Raftery et al. (1995) study (114), where models within six points of the lowest BIC were considered reasonable fits.

- **Visual goodness of fit:** Overlays of survival and hazards over time were visually inspected for goodness of fit to the KM data for both chemotherapy and cemiplimab + chemotherapy. This was not possible for pembrolizumab because the multiple KEYNOTE studies meant there was no single model population KM curve to compare against.

- **Compatibility of parametric model fit to reference curve and the NMA model (i.e., constant HR or two-step NMA):** Whilst all parametric models fit to the reference curve were considered compatible with the constant HR NMA, the

exponential distribution is constant over time and therefore was not considered when there was a violation of the PH assumption.

- **Base-case NMA model:** Whilst all parametric distributions evaluated in the two-step NMA were included in the cost-effectiveness model (CEM), priority in base case selection was given to those models considered optimal in the model selection for the NMA. The model selection for the NMA considered the plausibility of model fits within trials through visual inspection of the smoothed hazards and survival curves in the short term (maximum follow-up for each trial) and long term (360 months), and statistical goodness of fit in totality across trials in the network (i.e., sum of the AIC across all arms of all trials). Additionally, any findings regarding the plausibility of extrapolations for specific trials were considered with the aim of identifying the best overall distributions for the network of evidence (e.g., if the fit of a given model did not yield plausible within-trial extrapolations, such as if the modelled curves crossed while the data visually suggested separation, this distribution was eliminated). Where possible, the CEM model selection aligned with the NMA model selection, unless any evidence from the clinical validation criteria (see below) suggested this would be inappropriate to inform the CEM.

Clinical validation criteria:

- **External validation data OS:** Tails of the modelled OS functions were inspected to assess the clinical plausibility of the extrapolation beyond trial follow-up and 5-year OS estimates from the CEM were compared to external sources. As no real world data reporting long term survival for the population were identified, long term trial outcomes were evaluated for the PD-L1 ≥1% population, long-term trial outcomes were evaluated, acknowledging that there may be differences in populations which influence outcomes between external trials and the EMPOWER-Lung 3 target population. Five-year follow-up data from the KEYNOTE-407 trial evaluating pembrolizumab + chemotherapy in patients with previously untreated squamous advanced NSCLC was recently published, where five-year OS in patients with PD-

L1 ≥1% for pembrolizumab + chemotherapy and chemotherapy was 21.5% and 7.9%, respectively (115). The KEYNOTE-189 trial evaluating pembrolizumab + chemotherapy in patients with previously untreated non-squamous advanced NSCLC also recently published five-year follow-up, where five-year OS in patients with PD-L1 ≥1% for pembrolizumab + chemotherapy and chemotherapy was 24.7% and 15.3%, respectively (116). In both KEYNOTE trials, the OS curves for pembrolizumab + chemotherapy and chemotherapy alone remained separated across the 5-year follow-up period, validating the inclusion of a 5-year treatment effect for pembrolizumab + chemotherapy in the analysis. Previous NICE appraisals in the untreated NSCLC disease space were also evaluated to inform long-term survival estimates, where chemotherapy 5-year OS was predicted to be between 5-12% and IO combination 5-year OS to be between 10-20% (see Table 29) (40, 117). TA584 evaluating atezolizumab + bevacizumab + carboplatin + paclitaxel in the PD-L1 1-49% population suggested five-year OS for chemotherapy would range between 8-11% and five-year OS for atezolizumab + bevacizumab + carboplatin + paclitaxel would range between 10-13% (considerably lower than other estimates for IO combinations)(43). Recent conference materials from the British Thoracic Oncology Group were also reviewed (2021-2023), from which four studies were identified reporting real-world outcomes for pembrolizumab + chemotherapy (three studies) and chemotherapy (one study) (118-121). All four studies reported only median PFS and/or median OS rather than long-term PFS and OS, so external validation focused more on KEYNOTE five-year data and previous NICE appraisals. A comparison of patient characteristics of the three real-world studies evaluating pembrolizumab + chemotherapy versus the KEYNOTE studies is available in Appendix P.

- **Validation of extrapolations by UK clinical expert lung oncologists:** Base case model selection was validated by UK clinical experts (see Section B.3.8.5). They felt it was appropriate to extrapolate from the cemiplimab + chemotherapy evidence base and that they did not perceive any difference in efficacy data between EMPOWER-Lung 3 and KEYNOTE-189 or -407 studies.

- **Relationship between PFS and OS:** One of the key limitations of using a partitioned survival model structure is that PFS and OS are extrapolated as independent functions. This might lead to clinically implausible extrapolations, either due to PFS and OS curves crossing, or the model estimating a disproportionate post-progression survival benefit. The model was programmed so that PFS could not be greater than OS, i.e. the curves could not cross. This was also included as a clinical validation step at the model selection stage, as crossing of the curves could undermine confidence in the models selected for extrapolation. The estimated post-progression survival was also reviewed at the model selection stage, as extrapolations estimating a higher level of post-progression survival benefit may be subject to additional scrutiny.

- **General mortality:** A control was included to ensure that the mortality estimates in the modelled OS curves could not drop below the age-specific mortality rate estimated in the general age-matched UK population (122). The time point at which this control was applied was assessed at model selection stage to ensure OS did not intercept general mortality too early in the time horizon.

Table 29: Survival estimates reported in external trials, US and UK cost-effectiveness analyses evaluating immunotherapy combinations

TA	Year	Title	PD-L1	Histology	Chemotherapy survival	IO + chemotherapy survival
Clinical trials with five-year follow-up						
Novello et al. (115)	2023	Pembrolizumab Plus Chemotherapy in Squamous Non–Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study	PD-L1 ≥1%	Squamous	• 2 years: 8.5% (PFS) • Median PFS: 4.6 months • 5 years: 7.9% (OS) • Median OS: 12.8 months	• 2 years: 23.6% (PFS) • Median PFS: 8.3 months • 5 years: 21.5% (OS) • Median OS: 18.7 months
Garassino et al. (116)	2023	Pembrolizumab Plus Pemetrexed and Platinum in Non-squamous Non–Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study	PD-L1 ≥1%	Non-squamous	• 2 years: 4.5% (PFS) • Median PFS: 4.9 months • 5 years: 15.3% (OS) • Median OS: 11.3 months	• 2 years: 27.8% (PFS) • Median PFS: 10.9 months • 5 years: 24.7% (OS) • Median OS: 23 months
US cost-effectiveness analyses						
Insinga et al. (117)	2021	Cost-effectiveness of pembrolizumab + chemotherapy versus chemotherapy and pembrolizumab monotherapy in first-line treatment of NSCLC in the US – updated analyses with additional trial follow-up	Any PD-L1	Non-squamous and squamous NSCLC	• Squamous, 5 years: ~12% (OS), ~1% (PFS) • Non-squamous, 5 years: ~10% (OS), 0% (PFS)	• Squamous, 5 years: ~18% (OS), ~7% (PFS) • Non-squamous, 5 years: ~17% (OS) ~4% (PFS)
UK cost-effectiveness analyses[c]						
TA770 (previously TA600) (38)	2022	Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (recommended)	Any PD-L1	Squamous	• 5 years: 8-11% (OS), 3% (PFS)[a] • 10 years: 3-5% (OS)[a], 0% (PFS)[b] • 20 years: 0% (OS), 0% (PFS)[b]	• 5 years: 15-20% (OS), 10% (PFS)[a] • 10 years: 5-11% (OS)[a], 5% (PFS)[b] • 20 years: 2-4% (OS) [a], 4% (PFS)[b]
TA683 (previously TA557) (44)	2021	Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (recommended)	Any PD-L1	Non-squamous	• 5-11% OS at 5 years (4% considered very low in submission)	NR
TA584 (43)	2019	Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel for treating metastatic non-squamous non-small-cell lung cancer (recommended)	PD-L1 1-49%	Non-squamous	• 5 years: 8-11% (OS, reference to TA531) considered plausible • Company extrapolations resulted in 9-12% 5-year survival	• 5 years: 10-13% (OS)
UK real world evidence						
Ravindra et al. (118)	2021	Real-world outcomes using pembrolizumab plus pemetrexed-platinum in 1st line metastatic NSCLC compared to results	Any PD-L1	Non-squamous	--	• Median PFS: 7.1 months • Median OS: 8.7 months

		reported from KEYNOTE-189: a multicenter experience				
Ghoz et al. (119)	2023	Retrospective review of overall survival of combination platinum-pemetrexed-pembrolizumab in advanced non-squamous NSCLC in the context of PD-L1 score and presence of brain metastasis in the setting of a UK Cancer Centre	Any PD-L1	Non-squamous	--	• Median OS: 15 months
Pang et al. (120)	2023	Analyses of real-world data on patient outcomes in South Yorkshire, for patients with metastatic non-squamous lung cancer treated with pembrolizumab plus pemetrexed-platinum-based chemotherapy	Any PD-L1	Non-squamous	--	• Median PFS: 12 months • Median OS: 18 months
Lewis et al. (121)	2023	Outcomes for platinum doublet chemotherapy before and after first-line immune checkpoint inhibition in advanced non-small cell lung cancer (NSCLC)	Not reported	Not reported	• Median PFS: 6.5 months • Median OS: 9.8 months	--

[a]Based on ERG and NICE clinical advisor opinion; [b]Based on NICE clinical advisor; [c]Excludes NICE appraisals not culminating in a recommendation e.g. TA724 Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer (96).
IO, immunotherapy; NA, not applicable; NR, not reported; NSCLC, non-small cell lung cancer; NICE, National Institute for Health and Care Excellence; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TA, technology assessment

B.3.3.1.3 Extrapolation of treatment effects

Alternative options to modify the extrapolation of treatment effects were included in the CEM and can be applied to the OS and PFS curves for each treatment independently, for any treatment arm except for chemotherapy (i.e., the reference). These included:

- *Treatment waning effect (model base case):* the intervention hazard can be *'waned'* towards the hazard of the parametric function used to model OS and PFS for the chemotherapy arm, between user-defined start and end time points, after which the hazard of cemiplimab + chemotherapy and pembrolizumab + chemotherapy is assumed equal to the hazard for chemotherapy (HR vs. chemotherapy =1).

- *Continuation of treatment effect (called "Extrapolation of HR trend" in the model):* the hazard can be extrapolated over time horizon of the model.

- *Last HR carried forward*: The model includes functionality to allow for the time-varying hazard ratios to be held constant beyond a user-defined time point. This allows for time-varying hazard ratios to be included in the model where observed data were available to inform how treatment effect changes over time. In the case where the hazard ratio is monotonically decreasing, keeping the hazard ratio constant for the extrapolated time period is considered a conservative assumption. This option is not relevant to scenarios evaluating the constant HR NMA, as HRs are already constant over time.

B.3.3.2 Model selection

B.3.3.2.1 Progression-free survival

Alternative parametric models fit to the chemotherapy PFS from the PD-L1 ≥1%, any histology population of EMPOWER-Lung 3 (June 2022 DCO) are presented in terms of both survival and hazards over time in Figures 16 to 19.

Visual inspection of the distributions fit to the KM data demonstrated that the curves were all able to provide a good fit to the observed data. As the PFS data for the

chemotherapy arm from EMPOWER-Lung 3 were relatively mature (PFS at 2 years = 4.8%), minimal extrapolation was required, so the distributions all provided similar estimates of PFS over the time horizon. Assessment of the hazards over time indicated an increasing hazard rate for the first year followed by a decreasing hazard rate beyond 12 months. The log-logistic provided the best fit to this hazard trend, followed by the log-normal and generalised gamma.

The goodness of fit to the chemotherapy arm of EMPOWER-Lung 3 according to AIC and BIC criteria are reported in Table 30. The log-logistic provided the best fit according to both AIC and BIC statistics.

As described in Section B.2.9, a time-varying HR NMA was used to inform relative treatment effects for cemiplimab + chemotherapy and pembrolizumab + chemotherapy versus chemotherapy. The AIC across all study treatment arms was summed in order to help determine the best fitting model across studies (Table 31). Although the log-logistic was selected as the base case model, the generalised gamma and log-normal also provided a reasonable fit.

The models were also assessed in terms of predictive accuracy of the two-year landmark PFS and median PFS from the EMPOWER-Lung 3 trial (Table 32 and Table 33, respectively). The log-logistic most closely matched two-year PFS for chemotherapy from EMPOWER-Lung 3, the generalised gamma (fixed Q) most closely matched two-year PFS for cemiplimab + chemotherapy from EMPOWER-Lung 3 and the log-normal and generalised gamma (fixed Q) was most closely matched to two-year PFS mid-point between KEYNOTE-407 and KEYNOTE-189.

A summary of the overall model selection criteria is presented in Table 34. Following visual inspection of the distributions and hazards plots, assessment of the goodness of fit statistics and assessment of the predictive accuracy of the models to the 2-year landmark PFS, it was determined that the log-logistic model provided the best fit to the data, with the log-normal used as a scenario analysis. The log-logistic model was considered appropriate by UK clinical experts (see Section B.3.8.5). The base case

curves and curves used for the scenario analysis are shown in Figure 21 and Figure 22, respectively.

Figure 17 EMPOWER-Lung 3 (part 2; June 2022 data cut off) chemotherapy progression-free survival in the scenario for PD-L1 ≥1% any histology - parametric fits to hazard parametric fits to hazard

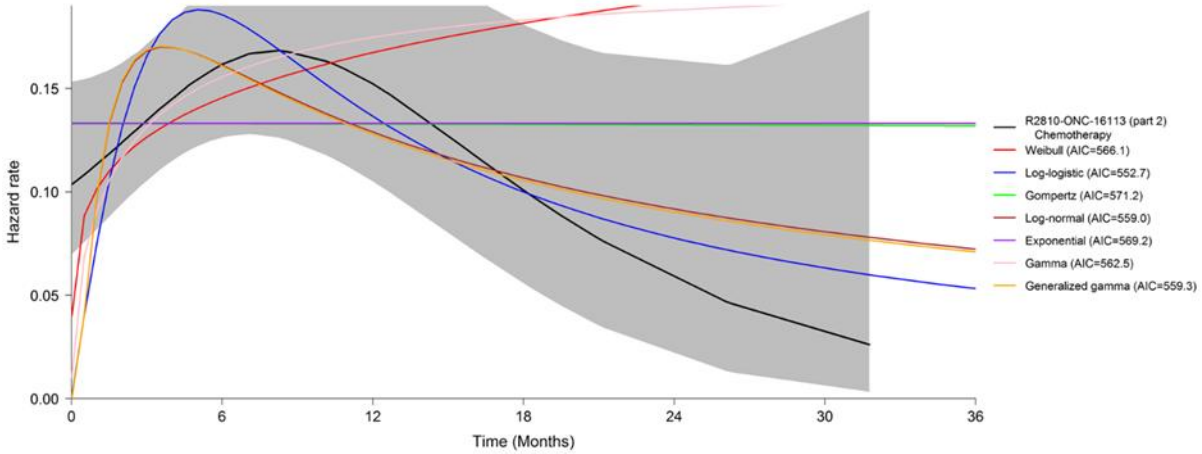


Figure 18 EMPOWER-Lung 3 (part 2; June 2022 data cut off) chemotherapy progression-free survival in the scenario for PD-L1 ≥1% any histology - parametric fits to hazard extrapolated to 30 years

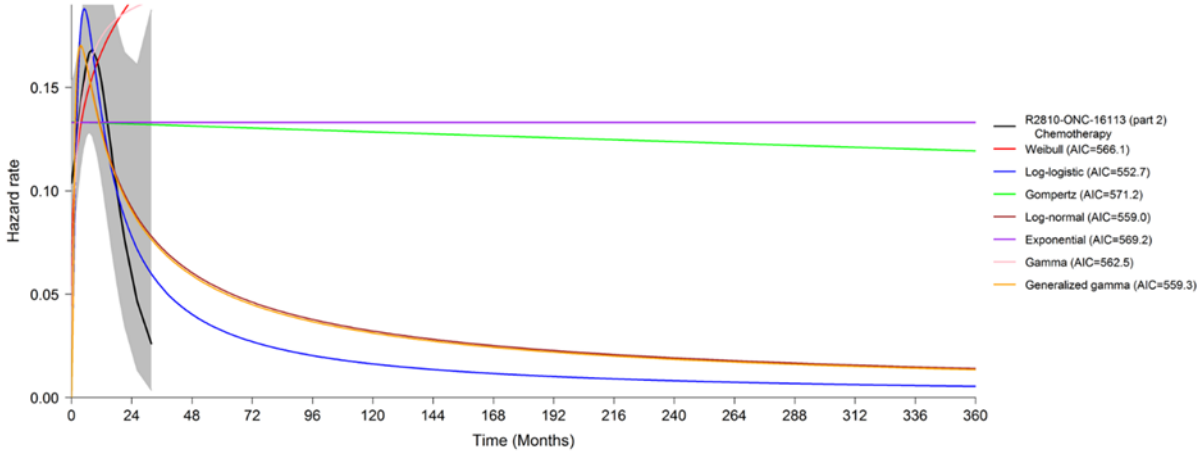


Figure 19 EMPOWER-Lung 3 (part 2; June 2022 data cut off) chemotherapy progression-free survival in the scenario for PD-L1 ≥1% any histology - parametric fits

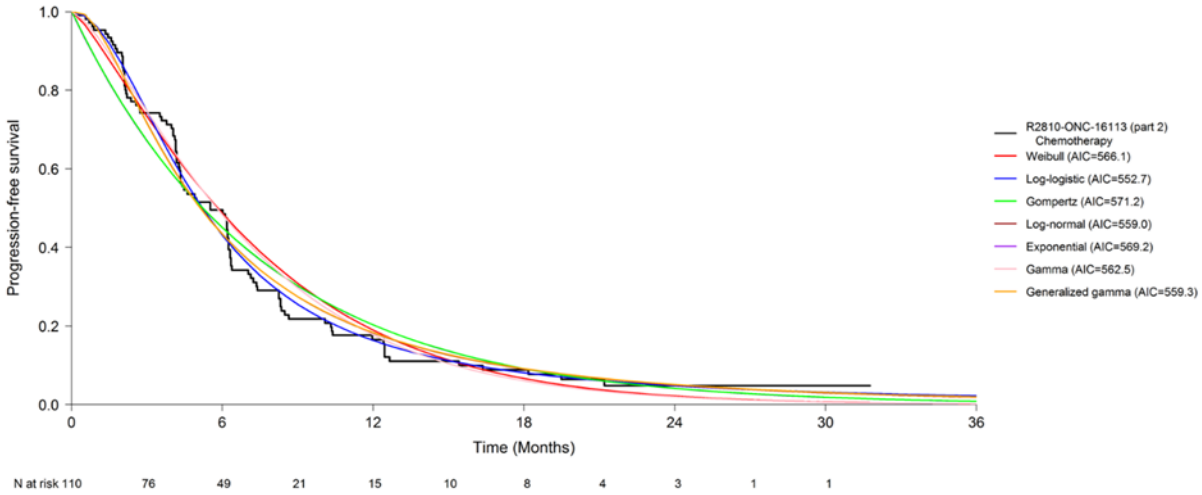


Figure 20 EMPOWER-Lung 3 (part 2; June 2022 data cut off) chemotherapy progression-free survival in the scenario for PD-L1 ≥1% any histology - parametric fits extrapolated to 30 years

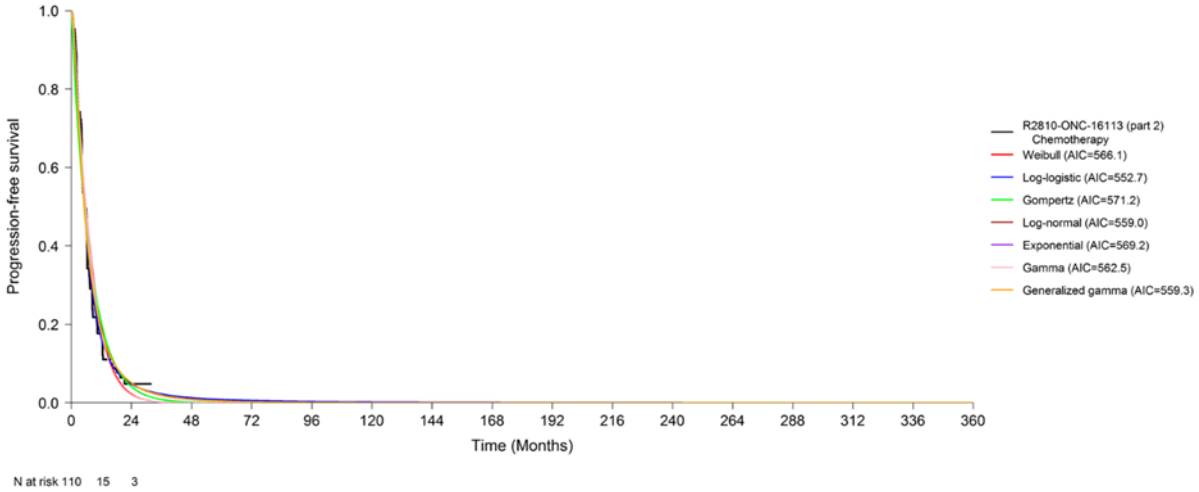


Table 30: Akaike's information criterion and Bayesian information criterion for standard parametric models fit to the PFS data for the chemotherapy arm of the PD-L1 ≥1%, any histology population from the EMPOWER-Lung 3 trial

	AIC[a]	BIC[b]	Rank
Exponential	569.23	571.93	6
Weibull	566.12	571.52	5
Gompertz	571.23	576.63	7
Log-normal	559.03	564.44	2
Log-logistic	**552.73**	**558.13**	**1**
Gamma	562.51	567.91	4
Generalised gamma (fixed Q)	559.25	564.65	3

The lowest AIC and BIC respectively are highlighted in bold orange. [a]Based on Burnham and Anderson (2004) (113) the statistical models within four points of the lowest AIC were considered reasonable fit (grey), [b]Based on Raftery et al (1995) (114), the statistical models within six points of the lowest BIC were considered reasonable fit (grey).
AIC, Akaike's information criterion; BIC, Bayesian information criterion.

Table 31: Goodness of fit statistics for the PFS NMA models, total AIC

Model	Goodness of fit, total AIC across studies	Assessment of NMA model
Exponential	6,649.02	Deprioritized (not one of the three lowest AICs)
Weibull	6,629.87	Deprioritized (not one of the three lowest AICs)
Gompertz	6,564.04	Excluded – extreme plateau in long-term survival for cemiplimab + chemotherapy
Log-normal	**6,519.42**	**Favoured** (second lowest total AIC)
Log-logistic	**6,488.58**	**Favoured** (lowest total AIC)
Gamma	6,638.30	Deprioritized (not one of the three lowest AICs)
Generalised gamma (fixed Q)	**6,520.00**	**Favoured** (third lowest total AIC)

The favoured AIC are highlighted in bold orange.
AIC, Akaike's information criterion; NMA, Network meta-analysis

Table 32: Two-year PFS estimates across treatment arms with each standard parametric distribution

Model	Chemotherapy (reference)	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy
Landmark survival at two years EMPOWER-Lung 3(86)	4.8%	23.4%	-
PD-L1 ≥1% external data sources (two-year PFS estimates)	KN-407(115) (sq) = 8.5% KN-189(116) (non-sq) = 4.5%	-	KN-407(115) (sq) = 23.6% KN-189(116) (non-sq) = 27.8%
Exponential	4.1%	22.8%	24.5%
Weibull	2.1%	21.9%	17.8%
Gompertz	4.1%	24.3%	19.8%
Log-normal	5.0%	23.1%	**25.0%**
Log-logistic	**4.8%**	21.5%	23.1%
Gamma	2.0%	21.3%	24.7%
Generalised gamma (fixed Q)	5.1%	**23.2%**	**25.0%**

Bold orange indicates values which align closest to external estimates.
AIC, Akaike's information criterion; non-sq, non-squamous; PFS, progression-free survival; sq, squamous.

Table 33: Median PFS estimates across treatment arms with each standard parametric distribution

Model	Chemotherapy (reference) (months)	Cemiplimab + chemotherapy (months)	Pembrolizumab + chemotherapy (months)
Landmark survival at two years EMPOWER-Lung 3(86)	5.5	8.3	-
PD-L1 ≥1% external data sources (median PFS, months)	KN-407(115) (sq) = 4.6 KN-189(116) (non-sq) = 4.9 Lewis et al.(121) = 6.5	-	KN-407(115) (sq = 8.3 KN-189(116) (non-sq) = 10.9 Ravindra et al.(118) (non-sq) = 7.1 Pang et al.(120) (non-sq) = 12
Exponential	**5.0**	11.0	**11.0**
Weibull	**5.0**	11.0	**10.0**
Gompertz	**5.0**	**10.0**	**10.0**
Log-normal	**5.0**	**10.0**	**10.0**
Log-logistic	**5.0**	**10.0**	**10.0**
Gamma	**5.0**	11.0	**12.0**
Generalised gamma (fixed Q)	**5.0**	**10.0**	**10.0**

Bold orange indicates values which align closest to external estimates. Median values are rounded to monthly model cycles.
AIC, Akaike's information criterion; non-sq, non-squamous; PFS, progression-free survival; sq, squamous.

Table 34: Validation summary table for PFS model selection for PD-L1 ≥1% any histology population

Model	Assessment of NMA model	Goodness of fit, chemotherapy EMPOWER-Lung 3		Two-year PFS estimates (based on extrapolations i.e., continuation of treatment benefit)			Decision
		AIC	BIC	Chemotherapy (reference)	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy	
Exponential	Deprioritized	569.23	571.93	4.1%	22.8%	24.5%	Deprioritized (based on NMA)
Weibull	Deprioritized	566.12	571.52	2.1%	21.9%	17.8%	Deprioritized (based on NMA)
Gompertz	Deprioritized	571.23	576.63	4.1%	24.3%	19.8%	Deprioritized (based on NMA)
Log-normal	**Favoured** (second lowest total AIC)	**559.03**	**564.44**	5.0%	23.1%	**25.0%**	**Scenario** (reasonable hazards and statistical goodness of fit, second favoured NMA model, improved survival projections)
Log-logistic	**Favoured** (lowest total AIC)	**552.73**	**558.13**	**4.8%**	21.5%	23.1%	**Base case** (best fit to chemotherapy hazards, best statistical goodness of fit to chemotherapy, favoured NMA model, plausible survival projections)
Gamma	Deprioritized	562.51	567.91	2.0%	21.3%	24.7%	Deprioritized based on NMA and chemotherapy hazards.
Generalised gamma (fixed Q)	**Favoured** (third lowest total AIC)	559.25	564.65	5.1%	**23.2%**	**25.0%**	Deprioritized based on NMA, could be considered as a scenario.

Bold orange indicates estimates which are favoured based on specified criteria (i.e., NMA model assessment, goodness of fit or external estimates).
AIC, Akaike information criterion; BIC, Bayesian information criterion; NMA, network meta-analysis; PFS, progression-free survival.

Figure 21: Base case PFS curves over a 36-month and lifetime time horizon: log-logistic, PD-L1 ≥1% any histology population (continuation of treatment benefit)

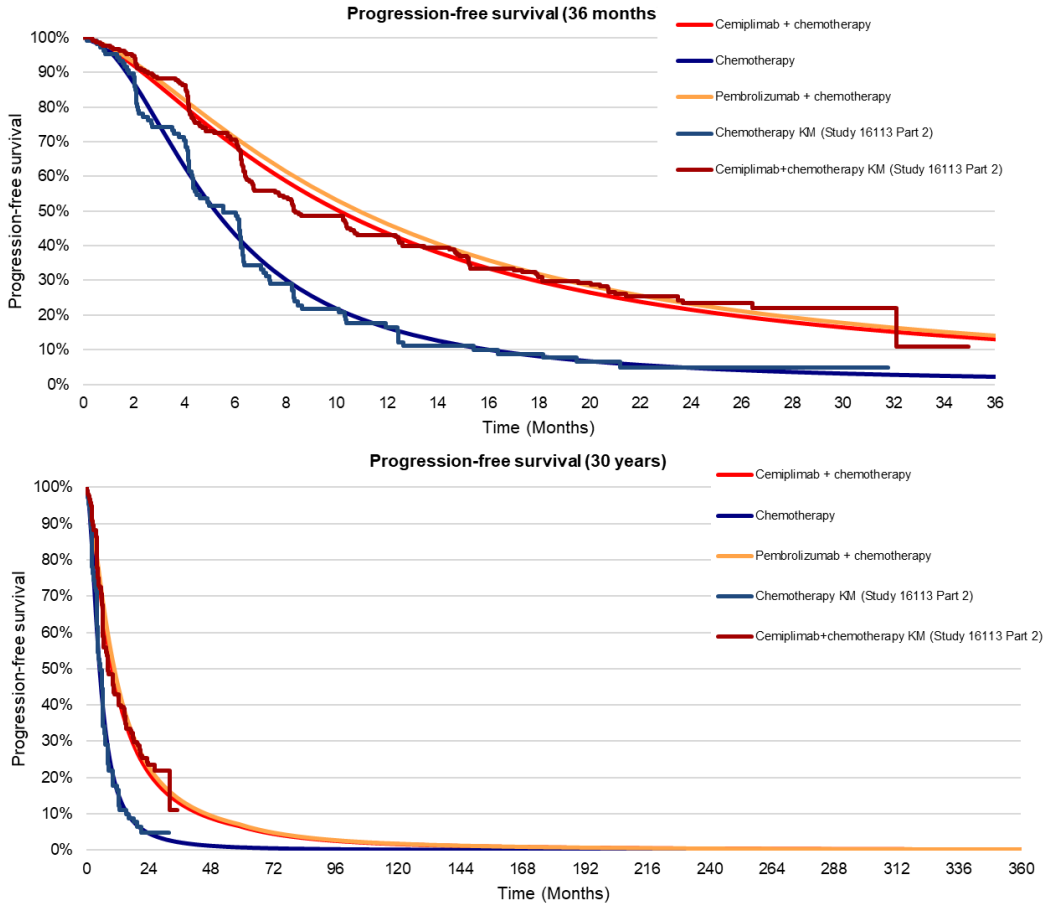
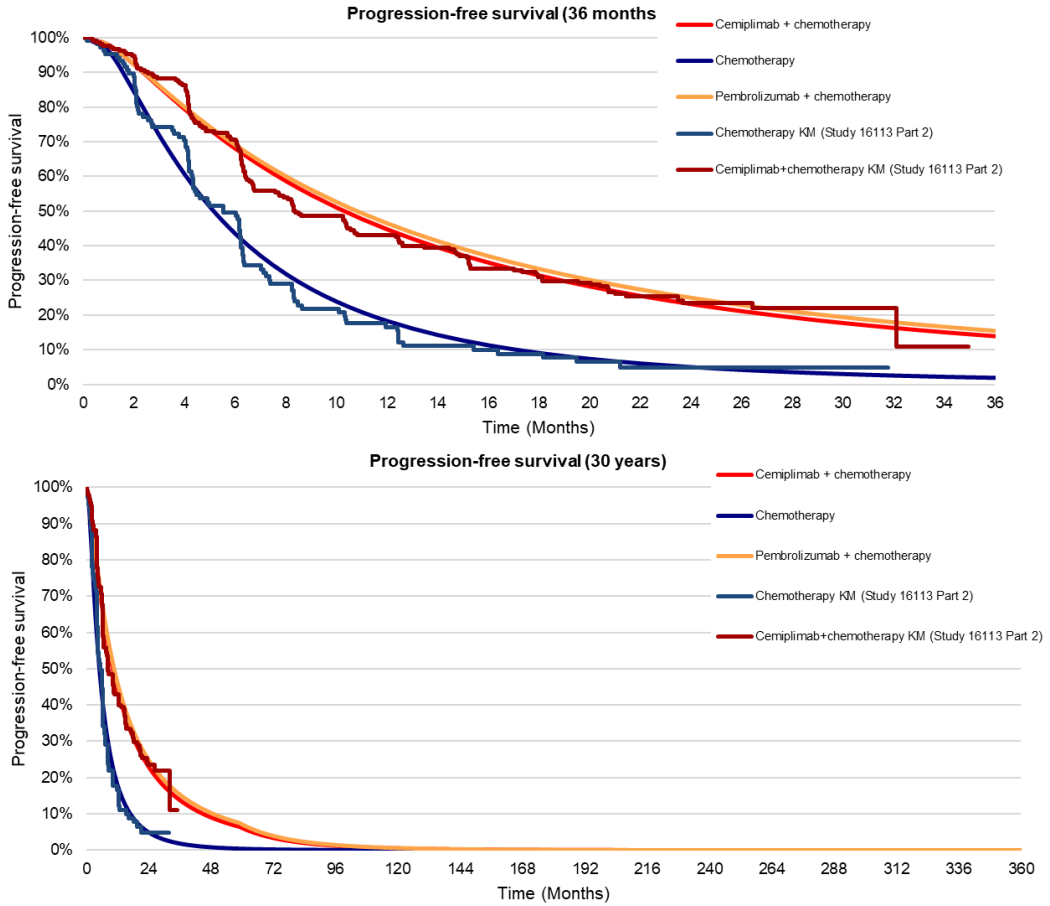


Figure 22: Scenario analysis: PFS curves over a 36-month and lifetime time horizon: log-normal, PD-L1 ≥1% any histology population (continuation of treatment benefit)



B.3.3.2.2 Overall survival

Alternative parametric models fit to the chemotherapy OS data for the PD-L1 ≥1%, any histology population from EMPOWER-Lung 3 (June 2022 DCO) are presented in terms of both survival and hazards over time in Figure 24, Figure 25 and Figure 26. Visual inspection of the distributions fit to the KM data demonstrated that the curves were all able to provide a reasonable fit to the observed data. Assessment of the hazards over time indicate an increasing hazard rate over the observed period. The Gompertz, gamma, and Weibull provide the best fit to this hazard trend.

The goodness of fit to the chemotherapy arm of EMPOWER-Lung 3 according to AIC and BIC criteria are reported in Table 35. The gamma provided the best fit according to AIC statistics and exponential provided the best fit according to BIC statistics, but most models were able to fit the observed data very well with AIC scores within four points of the best fitting and BIC scores within six points of the best fitting, with the exception of the log-normal model (both AIC and BIC).

As described in Section B.2.9, a time-varying HR from the 2-step multivariate NMA was used to inform relative treatment effects for cemiplimab + chemotherapy and pembrolizumab + chemotherapy versus chemotherapy. The AIC across all study treatment arms was summed in order to help determine the best fitting model across studies (Table 36). The log-logistic, Gompertz, and generalised gamma (fixed Q) provided the best fit across all study arms.

The five-year, ten-year and median survival estimates across all treatment arms from each model are shown in Table 37, Table 38 and Table 39, respectively. The five-year landmark survival for chemotherapy was validated against expected survival rates of 5-11% taken from recent NICE submissions TA724 (96), TA705 (40) and TA683 (44) and the reported five-year survival from KEYNOTE-407 (115) of 7.9% and KEYNOTE-189 (116) of 15.3%. The log-logistic, log-normal and generalised gamma (fixed Q) provided five-year survival estimates that fell within this range. The NICE TA531 (39) (pembrolizumab monotherapy) EAG preferred a model which predicted 1.5% of patients receiving chemotherapy to be alive at 10 years, which aligns closest with the

generalised gamma (fixed Q). The 5-year landmark survival for pembrolizumab + chemotherapy was validated against the expected survival rates of 15-20% taken from the NICE submission for pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (TA770) (38) and the reported 5-year survival from KEYNOTE-407 of 21.5% and KEYNOTE-189 of 24.7%. Both the log-logistic and log-normal provided five-year survival estimates that fell within the 15-20% range but all distributions underestimated survival compared to observed KEYNOTE-407 or 189.

A summary of the overall model selection criteria is presented in Table 40. Following visual inspection of the distributions, visual inspection of the hazard plots, assessment of the goodness of fit statistics, and validation of the five-year and ten-year survival, it was determined that the log-logistic model provided the best fit to the data, with the generalised gamma used as a scenario analysis. The log-logistic model was considered appropriate by UK clinical experts (see Section B.3.8.5). The curves used in the model base case and scenario analysis are shown over a 36 month and lifetime time horizon in Figure 27 and Figure 28**,** respectively.

Figure 23 EMPOWER-Lung 3 (part 2; June 2022 data cut off) chemotherapy overall survival in the scenario for PD-L1 ≥1% any histology - parametric fits to hazard

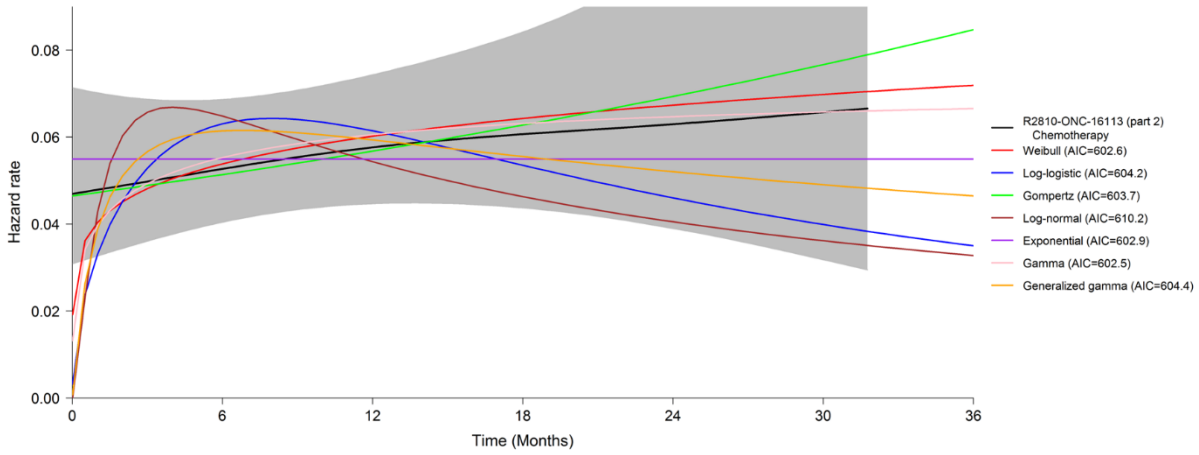


Figure 24: EMPOWER-Lung 3 (part 2; June 2022 data cut off) chemotherapy overall survival in the scenario for PD-L1 ≥1% any histology - parametric fits to hazard extrapolated to 30 years

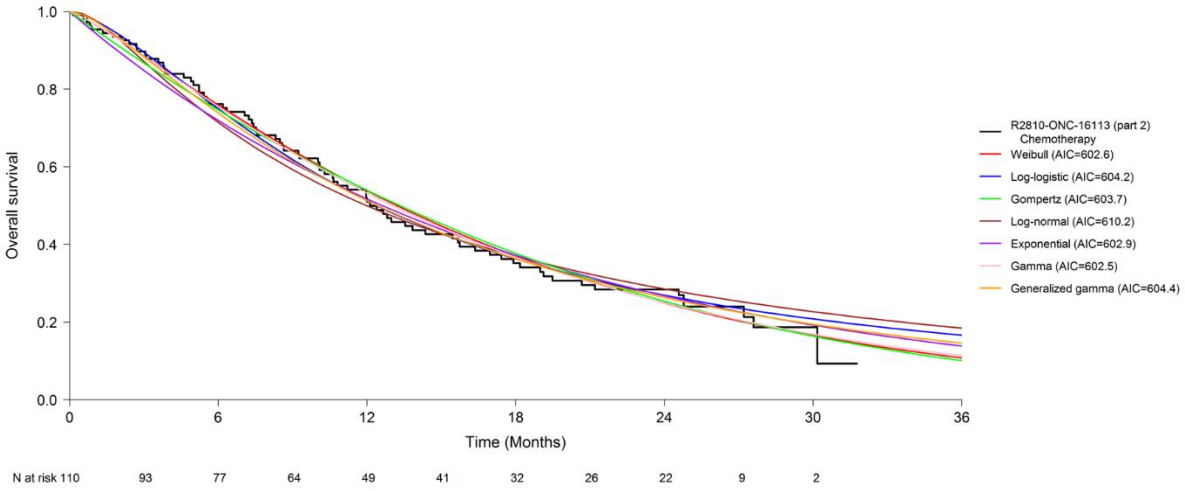


Figure 25: EMPOWER-Lung 3 (part 2; June 2022 data cut off) chemotherapy overall survival in the scenario for PD-L1 ≥1% any histology - parametric fits

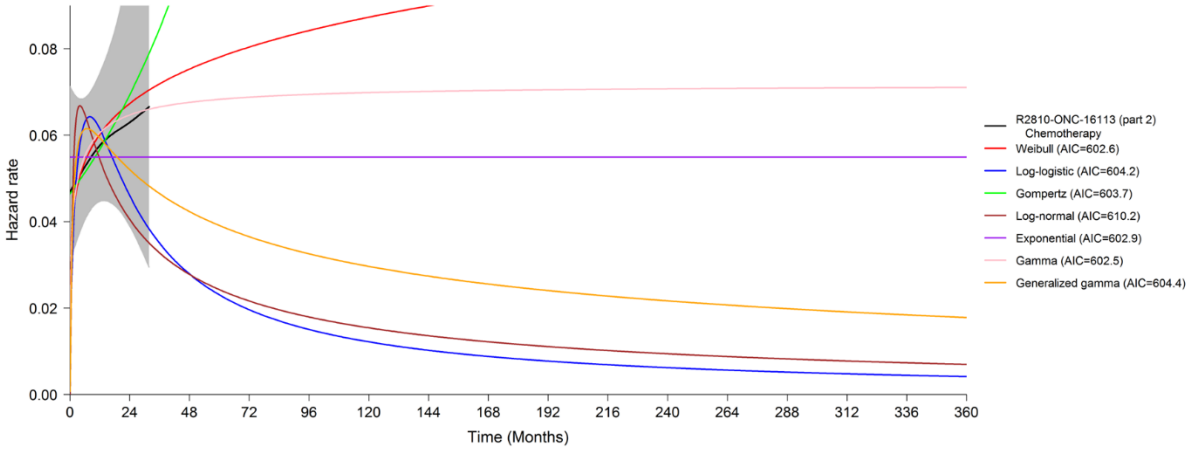


Figure 26: EMPOWER-Lung 3 (part 2; June 2022 data cut off) chemotherapy overall survival in the scenario for PD-L1 ≥1% any histology - parametric fits extrapolated to 30 years

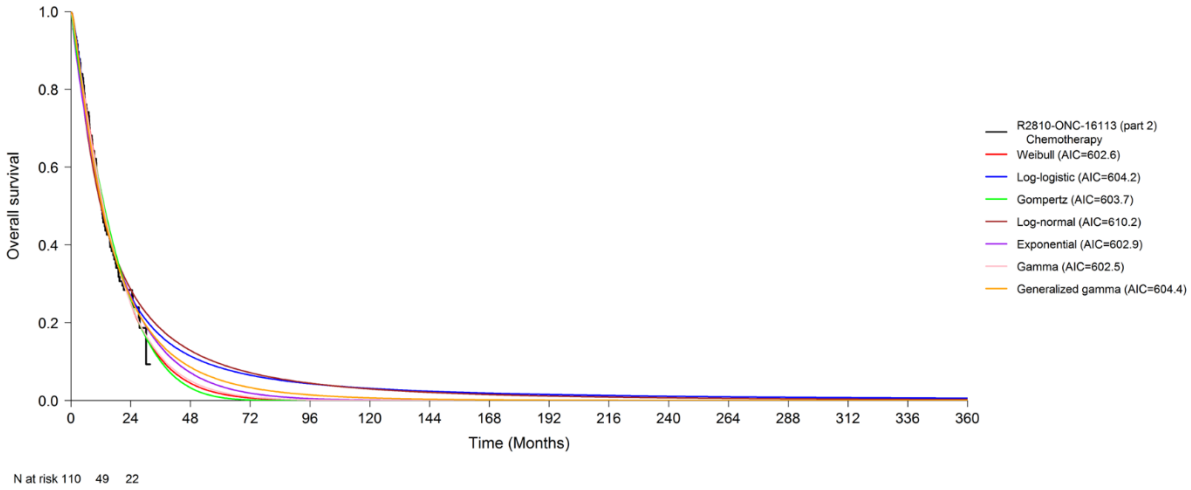


Table 35: Akaike's information criterion and Bayesian information criterion for standard parametric models fit to the OS data for the chemotherapy arm of the EMPOWER-Lung 3 trial

	AIC[a]	BIC[b]	Joint rank
Exponential	602.89	**605.59**	**1**
Weibull	602.61	608.01	3
Gompertz	603.71	609.11	4
Log-normal	610.18	615.58	7
Log-logistic	604.20	609.60	5
Gamma	**602.52**	607.92	2
Generalised gamma (fixed Q)	604.44	609.84	6

The lowest AIC and BIC respectively are highlighted in bold orange. a) Based on Burnham and Anderson (2004) (113) the statistical models within four points of the lowest AIC were considered reasonable fit (grey), b) Based on Raftery et al (1995) (114), the statistical models within six points of the lowest BIC were considered reasonable fit (grey).
AIC, Akaike's information criterion; BIC, Bayesian information criterion.

Table 36: Goodness of fit statistics for the OS NMA models

Model	Goodness of fit, total AIC across studies	Assessment of NMA model
Exponential	6,955.24	Excluded – PH violation
Weibull	6,951.62	Deprioritized (not one of the three lowest AICs)
Gompertz	**6,928.61**	**Favoured** (second lowest total AIC)
Log-normal	6,958.01	Deprioritized (not one of the three lowest AICs)
Log-logistic	**6,925.18**	**Favoured** (lowest total AIC)
Gamma	6,957.13	Deprioritized (not one of the three lowest AICs)
Generalised gamma (fixed Q)	**6,933.79**	**Favoured** (third lowest total AIC)

The favoured AIC are highlighted in bold orange.
AIC, Akaike's information criterion; NMA, Network meta-analysis

Table 37: Five-year OS estimates across treatment arms with each standard parametric distribution

Model	Chemotherapy (reference)	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy
Any-PD-L1 external data sources (five-year OS estimates)	NICE TA724(96) (sq/nsq), TA705(40) (sq/nsq), TA683(44) (nsq): **5-11% and** TA770(38) (nsq)	No external estimates	TA770(38) (nsq) and Insinga 2021 (US, sq/nsq): **15-20%**
PD-L1 ≥1% external data sources (five-year OS estimates)	KN-407(115) (squamous) = **7.9%** KN-189(116) (non-squamous) = **15.3%**	Not reported	KN-407(115) (squamous) = **21.5%** KN-189(116) (non-squamous) = **24.7%**
Exponential	3.7%	17.2%	11.9%
Weibull	1.8%	11.9%	6.5%
Gompertz	0.8%	5.7%	3.4%
Log-normal	**9.4%**	25.0%	**19.8%**
Log-logistic	**8.4%**	21.5%	**17.6%**
Gamma	2.2%	13.6%	9.2%
Generalised gamma (fixed Q)	**5.3%**	19.5%	14.6%

Bold orange indicates values which align closest to external estimates. Insinga 2021 is a US CE analysis.
NICE, National Institute for Health and Care Excellence; nsq, non-squamous; OS, overall survival; PD-L1, programmed death-ligand 1; sq, squamous

Table 38: Ten-year OS estimates across treatment arms with each standard parametric distribution

Model	Chemotherapy (reference)	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy
Any-PD-L1 external data sources (ten-year OS estimates)	TA531 (39) (EAG) – **1.5%** Insinga et al. (117) (US, sq/nsq): **~5-8% ;** TA770(38) (nsq) – **3-5%**	Not reported	Insinga et al. (117) (US, sq/nsq): **~8-10%;** TA770(38) (nsq) – **5-11%**
Exponential	0.1%	3.0%	1.4%
Weibull	0.0%	0.8%	0.2%
Gompertz	0.0%	0.0%	0.0%
Log-normal	**3.0%**	11.9%	**8.2%**
Log-logistic	**3.1%**	9.5%	7.2%
Gamma	0.0%	1.4%	0.6%
Generalised gamma (fixed Q)	**0.7%**	5.9%	3.4%

Bold orange indicates values which align closest to external estimates. Insinga 2021 is a US CE analysis
EAG, evidence assessment group; NICE, National Institute for Health and Care Excellence; nsq, non-squamous; OS, overall survival; PD-L1, programmed death-ligand 1; sq, squamous

Table 39: Median OS estimates across treatment arms with each standard parametric distribution

Model	Chemotherapy (reference) (months)	Cemiplimab + chemotherapy (months)	Pembrolizumab + chemotherapy (months)
Landmark survival at two years EMPOWER-Lung 3(86)	12.1	23.5	-
PD-L1 ≥1% external data sources (median O, months)	KN-407(115) (sq) = 12.8 KN-189(116) (non-sq) = 11.3 Lewis et al.(121) = 9.8	-	KN-407(115) (sq = 18.7 KN-189(116) (non-sq) = 23.0 Ravindra et al.(118) (non-sq) = 8.7 Ghoz et al.(119) (non-sq) = 15 Pang et al.(120) (non-sq) = 18
Exponential	**12.0**	**23.0**	**19.0**
Weibull	13.0	**23.0**	**19.0**
Gompertz	13.0	**23.0**	**19.0**
Log-normal	11.0	**23.0**	**20.0**
Log-logistic	**12.0**	**23.0**	**20.0**
Gamma	13.0	**23.0**	**20.0**
Generalised gamma (fixed Q)	**12.0**	**23.0**	**20.0**

Bold orange indicates values which align closest to external estimates. Medians rounded to monthly model cycles.
AIC, Akaike's information criterion; non-sq, non-squamous; PFS, progression-free survival; sq, squamous.

Table 40: Validation summary table for OS model selection for the PD-L1 ≥1% any histology population

Model	Assessment of NMA model	Goodness of fit, chemotherapy EMPOWER-Lung 3		Five-year OS estimates (based on extrapolations i.e., continuation of treatment benefit)			Ten-year OS estimates (based on extrapolations i.e., continuation of treatment benefit)			Decision
		AIC	BIC	Chemotherapy (reference)	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy	Chemotherapy (reference)	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy	
Exponential	Excluded due to PH violations	602.89	605.59	3.7%	17.2%	11.9%	0.1%	3.0%	1.4%	Excluded (PH violations)
Weibull	Deprioritized	602.61	608.01	1.8%	11.9%	6.5%	0.0%	0.8%	0.2%	Deprioritized based on NMA

Model	Assessment of NMA model	Goodness of fit, chemotherapy EMPOWER-Lung 3		Five-year OS estimates (based on extrapolations i.e., continuation of treatment benefit)			Ten-year OS estimates (based on extrapolations i.e., continuation of treatment benefit)			Decision
		AIC	BIC	Chemotherapy (reference)	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy	Chemotherapy (reference)	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy	
Gompertz	Favoured (second lowest AIC)	603.71	609.11	0.8%	5.7%	3.4%	0.0%	0.0%	0.0%	Deprioritized (chemotherapy and pembrolizumab + chemotherapy lower than literature).
Log-normal	Deprioritized	610.18	615.58	**9.4%**	25.0%	**19.8%**	**3.0%**	11.9%	**8.2%**	Deprioritized based on NMA, poorer visual fit of extrapolations to KM's
Log-logistic	Favoured (lowest AIC)	604.20	609.60	**8.4%**	21.5%	**17.6%**	**3.1%**	9.5%	7.2%	**Base case** (favoured NMA model, AIC/BIC similarity, survival projections)
Gamma	Deprioritized	602.52	607.92	2.2%	13.6%	9.2%	0.0%	1.4%	0.6%	Deprioritized based on NMA
Generalised gamma (fixed Q)	Favoured (third lowest AIC)	603.44	613.54	**5.3%**	19.5%	14.6%	0.7%	5.9%	3.4%	**Scenario** (third favoured NMA model, AIC/BIC, survival projections)

Bold orange indicates estimates which are favoured based on specified criteria (i.e., NMA model assessment, goodness of fit or external estimates).
AIC, Akaike information criterion; BIC, Bayesian information criterion; NMA, network meta-analysis; PFS, progression-free survival.

Figure 27: Base case OS curves over a 36-month and lifetime time horizon: log-logistic, PD-L1 ≥1% any histology population

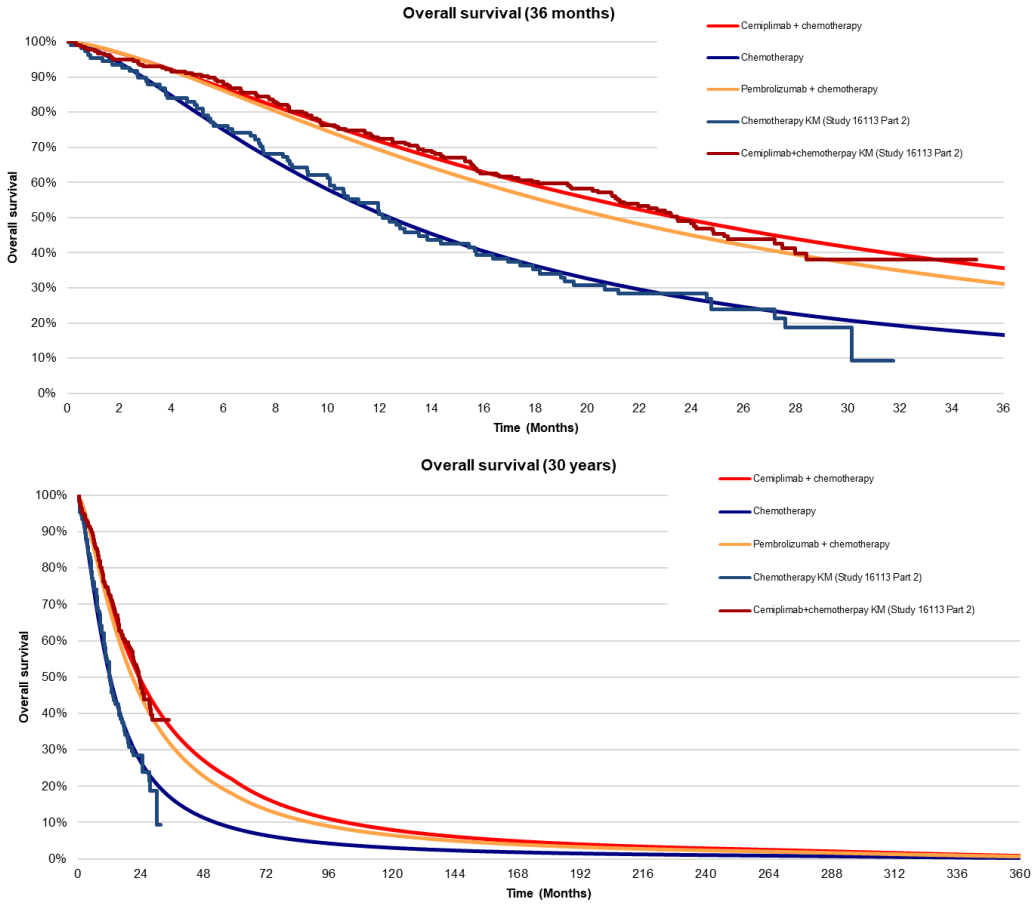
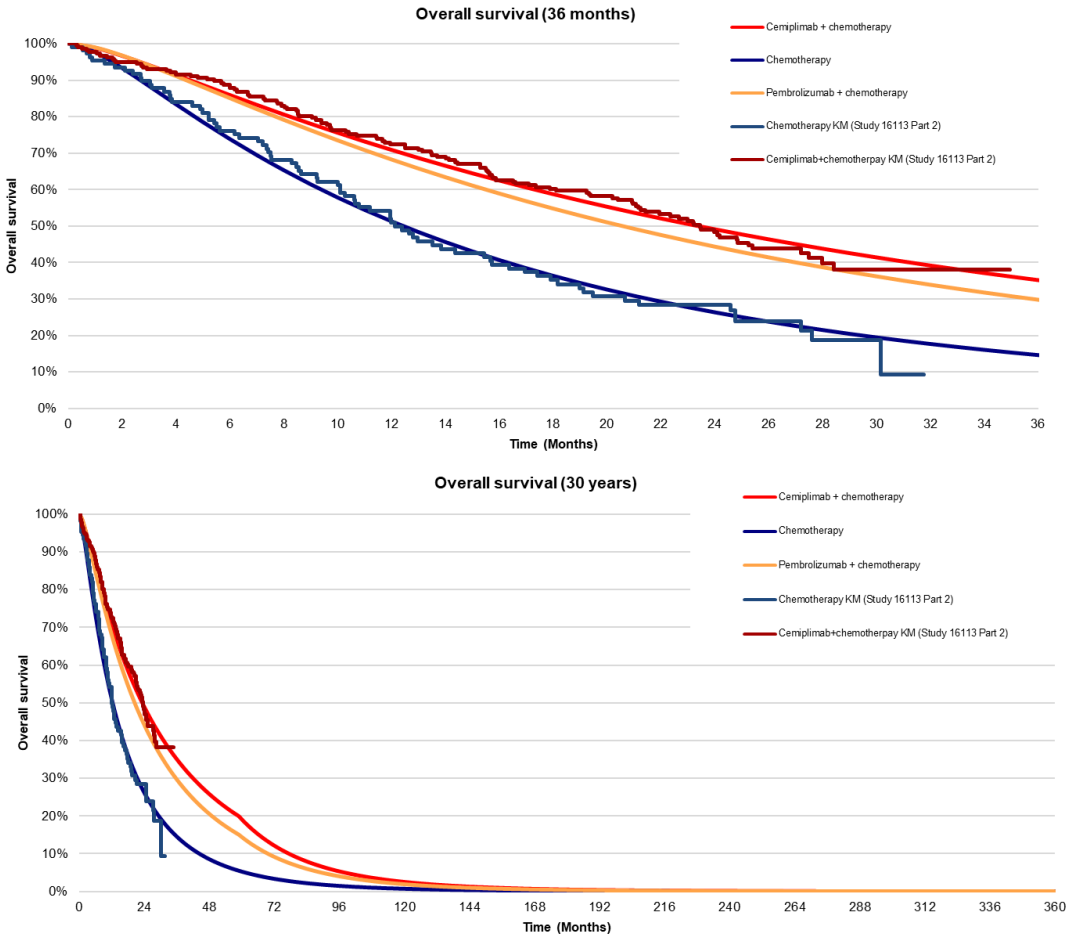


Figure 28: Scenario analysis: OS curves over a 36-month and lifetime time horizon: generalised gamma, PD-L1 ≥1% any histology population



B.3.3.3 Modelled long-term treatment effect

Patients in EMPOWER-Lung 3 received cemiplimab for a maximum of 108 cycles (i.e., 24 months). Similarly, patients in KEYNOTE-407 and 189 received pembrolizumab for a maximum of 24 months. In the NICE appraisals for pembrolizumab + chemotherapy (TA683 and TA770), the continuation of treatment effect after treatment stopping was discussed. In TA683 the committee accepted a treatment waning from three to five years after treatment was started while in TA770, the committee accepted a treatment effect lasting to five years based on five-year follow-up from KEYNOTE-407 (38, 44). Thus, in the base case analysis, which includes five-year follow-up from the KEYNOTE studies in the NMA, treatment benefit was assumed to continue to five years after which

hazards for cemiplimab + chemotherapy and pembrolizumab + chemotherapy were assumed equal to chemotherapy. This assumption was validated by UK clinical experts (see Section B.3.8.5), who confirmed that patients continue to benefit following two years of IO treatment, with T-cell activation through three to five years. Applying the same assumption for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy was considered appropriate as experts did not perceive any difference in efficacy data between EMPOWER-Lung 3 and KEYNOTE-189 or -407 studies. Scenario analyses evaluating treatment effect up to three years after which hazards for cemiplimab + chemotherapy and pembrolizumab + chemotherapy were assumed equal to chemotherapy, and a waning of treatment effect between three and five years were explored.

A summary of the modelling choices underpinning the modelling of PFS and OS is provided in Table 41.

Table 41: Summary of modelling choices for PFS and OS in the PD-L1 ≥ 1% any histology population and subgroups

Scenario	PFS		OS	
	Baseline survival curve	NMA	Baseline survival curve	NMA
PD-L1 ≥ 1%, any histology				
Base case	log-logistic	2-step multivariate NMA log-logistic fixed effects, with non-informative priors	log-logistic	2-step multivariate NMA log-logistic fixed effects, with non-informative priors
Scenario analysis 1	log-normal	2-step multivariate NMA log-normal fixed effects, with non-informative priors	Generalised gamma (two parameter fixed Q)	2-step multivariate NMA generalised gamma fixed effects, with non-informative priors
Scenario analysis 2	log-logistic	Constant HR NMA fixed effects, with non-informative priors	As per base case	As per base case
PD-L1 1-49%, squamous histology				
Base case (subgroup)	log-logistic	2-step multivariate NMA log-logistic fixed effects, with non-informative priors	exponential	2-step multivariate NMA exponential fixed effects, with non-informative priors
Scenario analysis 1 (subgroup)	log-logistic	Constant HR NMA fixed effects, with non-informative priors	exponential	Constant HR NMA fixed effects, with non-informative priors
PD-L1 ≥ 50%, squamous histology				
Base case (subgroup)	log-logistic	2-step multivariate NMA log-logistic fixed effects, with non-informative priors	gamma	2-step multivariate NMA gamma fixed effects, with non-informative priors
Scenario analysis 1 (subgroup)	log-logistic	Constant HR NMA fixed effects, with non-informative priors	gamma	Constant HR NMA fixed effects, with non-informative priors
PD-L1 1-49% non-squamous				
Base case (subgroup)	log-logistic	2-step multivariate NMA log-logistic fixed effects, with non-informative priors	log-logistic	2-step multivariate NMA log-logistic fixed effects, with non-informative priors

Scenario analysis 1 (subgroup)	log-logistic	Constant HR NMA fixed effects, with non-informative priors	log-logistic	Constant HR NMA fixed effects, with non-informative priors
PD-L1 ≥50%, non-squamous				
Base case (subgroup)	log-logistic	2-step multivariate NMA log-logistic fixed effects, with non-informative priors	log-logistic	2-step multivariate NMA log-logistic fixed effects, with non-informative priors
Scenario analysis 1 (subgroup)	log-logistic	2-step multivariate NMA log-logistic fixed effects, with non-informative priors	log-logistic	2-step multivariate NMA log-logistic fixed effects, with non-informative priors

HR, hazard ratio; NMA, network meta-analysis.

B.3.3.4 Adverse reactions

The model included Grade 3+ AEs which occurred in ≥5% of patients in any treatment arm within the relevant trials considered in the NMA evidence base (i.e., EMPOWER Lung-3 RCT for cemiplimab + chemotherapy and KEYNOTE-189/407 studies for pembrolizumab + chemotherapy). Grade 1 to 2 AEs were not considered in the model, as they are generally understood to have lower cost and/or QoL implications, whereas Grade 3+ AEs are more burdensome on both the healthcare system and have a greater impact on patient HRQoL. AEs occurred in ≥5% of patients were employed to avoid a random selection of AEs and to ensures a more manageable list of AEs in the model.

Grade 3+ AEs for the PD-L1 ≥1%, any histology and PD-L1 1-49%, any histology subgroups were only reported in the EMPOWER-Lung 3 trial (see Table 42) (86). To ensure AEs were derived from similar populations across the trials, AEs in the CEM were based on the any PD-L1, any histology (i.e., MHRA label) population and remain consistent regardless of the PD-L1 threshold selection in the model. For the squamous and non-squamous subgroups, AE rates by histology were more widely reported and suggested a difference in AE rates between the squamous and non-squamous subgroups. Thus, for the squamous or non-squamous subgroups, AE rates are based on the squamous (any PD-L1) and non-squamous (any PD-L1) populations (reported in Appendix E).

Frequencies of Grade 3+ treatment-emergent AEs (TEAEs) were sourced from the clinical study report for EMPOWER-Lung 3 for cemiplimab + chemotherapy. For pembrolizumab + chemotherapy, TEAEs were reported for Grade 3+ in the KEYNOTE-189 and KEYNOTE-407 trials and were weighted by histology reported in the EMPOWER-Lung 3 trial. The frequency of AEs included in the model was validated by UK clinical expert follow-up interview (see Section B.3.8.5). Table 43 presents the AEs for all treatments included in the base case analysis.

As mentioned previously in Section B.1.3, the use of pemetrexed as part of a chemotherapy regimen, or use of higher dose (AUC6) carboplatin, is associated with significant toxicity and resulting AEs. Cemiplimab can be used in combination with

chemotherapy regimens that do not contain pemetrexed or with lower dosages of carboplatin. This flexibility in the chemotherapy backbone is not an option for patients treated with pembrolizumab + chemotherapy. Despite these potential advantages, the analysis assumed the same chemotherapy backbone regimen. While this may result in a misalignment between the AEs reported in the source studies and the chemotherapy regimens assumed in the model, this uncertainty was addressed in a scenario analysis in which AE costs and disutilities are removed from the model.

Table 42 Trial data availability for grade 3+ adverse event rates by PD-L1 expression level for any histology

PD-L1 expression and histology	EMPOWER-Lung 3 (86)	KN-189, KN-407 (115, 116)
Any PD-L1, any histology	✓	✓[a]
PD-L1 ≥1%, any histology	✓	NA
PD-L1 1-49%, any histology	✓	NA

Green checkmarks indicate relevant safety outcome data availability by PD-L1 expression and histology; NA indicates the absence of publicly reported Grade 3+ AE outcome data by the specified PD-L1 expression and histology. a) safety data from the KEYNOTE-189 and KEYNOTE-407 trials weighted by split of non-squamous and squamous in EMPOWER-Lung 3. Thus, for the squamous or non-squamous subgroups, AE rates are based on the squamous (any PD-L1) and non-squamous (any PD-L1) populations (reported in Appendix)
KN, KEYNOTE; PD-L1, programmed death-ligand 1.

Table 43 Grade 3+ adverse events for cemiplimab + chemotherapy and pembrolizumab + chemotherapy

Adverse event	Cemiplimab + chemotherapy (86)	Pembrolizumab + chemotherapy (115, 116)
Anaemia	**10.90%**	**17.65%**
Fatigue	2.88%	**6.38%**
Neutropenia	**6.41%**	**19.46%**
Thrombocytopenia	3.21%	**8.48%**

Bolded values indicate ≥5% frequency.

Adverse event data was also identified as part of the HRQOL SLR discussed in Section B.3.4.4, with full details in Appendix H. A summary of the results including adverse events is presented in

Table 47.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data used in the cost-effectiveness analysis

Health state utility values (HSUVs) were included in the model for the progression-free and progressed disease health states. Because quality of life is assumed to be linked to disease progression, not the treatment received, pooled EMPOWER-Lung 3 ITT population values across treatment arms were used in the HSUV analysis.

The NICE reference case could not be met because EQ-5D data were not directly collected in the EMPOWER-Lung 3 trial. The next best alternative approach in accordance the NICE DSU technical support document 22 guidance (123) was therefore taken.

Base case HSUVs were derived from oncology-specific EORTC-QLQ C30 data collected in EMPOWER-Lung 3 which were mapped to the EQ-5D-3L using a UK tariff (described in Section B.3.4.3). A utility of 0.765 (standard error [SE] 0.005) was calculated for the progression-free health state and a utility of 0.723 (SE 0.010) for the post-progression health state (Table 44). The PFS utility value, as expected, lies below the age and gender population norm of 0.84(124), and the utility values were confirmed to have face validity by UK clinical expert lung oncologists. Furthermore, these values are of similar magnitude to publicly available values accepted in other NICE appraisals in this population, as shown in Table 44.

Seven alternative HSUV sources were identified in the SLR update (see Table 47), however, these were not included within the cost-effectiveness analysis due to four of the sources reporting HSUV from monotherapy studies (95, 99, 100, 125), which were indicated by UK clinical expert lung oncologists to be less representative of expected HSUV of IO + chemotherapy treatments. TA724 and TA770 only included redacted HSUVs (38, 96) ,and the final source used the same outcomes from TA584, based on IMPower150 outcomes (104), which are already included as a scenario within this submission.

The sensitivity of the model to different utility values was therefore tested by conducting scenario analyses using alternative published utility values. While all the values in Table 44 are available in the model, only the results using the utilities from Impower 150 are provided in Section B.3.8.3 as the other utility values from Table 44 also resulted in dominance for cemiplimab + chemotherapy.

Table 44 Health state utility values in the economic model

Source	Response status	Utility value, mean (SE)
EMPOWER Lung-3 EORTC-QLQ C30 mapped to EQ-5D-3L utility	Progression-free	0.765 (0.005)
	Progressed	0.723 (0.010)
NICE TA584 (Impower 150) (43)	Progression-free	0.710 (0.005)
	Progressed	0.690 (0.015)
NICE TA584 (scenario analysis, Nafees et al. 2008) (43)	Progression-free	0.673 (0.070)
	Progressed	0.473 (0.022)
NICE TA584 (scenario analysis, Chouaid et al. 2013) (43)	Progression-free	0.710 (0.023)
	Progressed	0.670 (0.041)

SE, standard error.

B.3.4.2 Quality of life impact of age

Guidance from NICE recommends adjusting utility values if extrapolating over long time horizons so that they reflect a decrease in HRQoL as seen in the general population and to ensure that utility values do not exceed that of the general population at a given age (109). As assuming baseline utility values remain constant over the time horizon of the model may inflate the incremental QALYs gained, the base case analysis included an adjustment of HSUVs by age.

To align with the approach suggested by Hernandez et al. 2022 (124) (i.e., the DSU report for age and sex adjustment of utilities in the UK), the age-related utility decrement in the base case was based on the Health Survey for England data from 2014 (n = 7,085) and employed adjusted limited dependent variable mixture models to estimate EQ-5D-3L utilities separately for males and females according to age. The estimated EQ-5D-3L models by age and sex were used to generate utilities by age and sex. These utilities were included in the CEM to calculate a utility multiplier for each model cycle based on the age and sex of the cohort. The adjustment was applied in the model

based on the increasing average age of the patient cohort, assuming a starting age at baseline of 62 years based on the EMPOWER-Lung 3 trial.

B.3.4.3 Mapping

Patient reported outcomes were collected in EMPOWER-Lung 3 using both the EORTC QLQ-C30 and EORTC QLQ-LC13 instruments, the first being a questionnaire developed specifically for cancer patients and the second specifically for lung cancer patients.. To estimate the utility pre- and post-progression for patients with advanced NSCLC EORTC QLQ-C30 individual patient data (IPD) from EMPOWER-Lung 3 were mapped to the EQ-5D-3L values. Utilities were estimated using EORTC QLQ-C30 rather than EORTC QLQ-LC13 data because the mapping of EORTC QLQ-C30 to EQ-5D-3L has precedent in prior NSCLC TAs (TA802 and TA911). The mean EORTC QLQ-C30 response using the global health status scale are reported in Figure 29.

Targeted literature searches were performed to identify algorithms that mapped EORTC QLQ-C30 to EQ-5D (either 3L or 5L). First, the Health Economics Research Centre (HERC) database of mapping studies was searched to identify existing algorithms and systematic reviews. Secondly, the PubMed database was searched to identify any missing algorithms in the HERC database. Thirdly, NICE technology appraisal submissions in oncology were queried to provide additional context on existing algorithms. Lastly, references from select review articles identified in the searches of PubMed involving mapping algorithms were manually searched to identify any studies not captured in the above searches.

A total of 27 publications presenting 27 unique mapping algorithms were identified from the targeted literature searches (original December 2020; update February 2023) which were evaluated in patients with various cancers and from different sources of data, including RCTs, cohort studies, and clinical databases. The most relevant algorithms for the UK were prioritized. Both EQ-5D-3L and EQ-5D-5L were considered, but the mapping of EORTC QLQ-C30 to EQ-5D-3L was prioritized for the NICE reference case (109).

The Longworth et al. (2014) algorithm was selected as the most appropriate algorithm for the base case analysis due to its population including all cancers, good predictive qualities, and ability to incorporate different tariffs (126). Two out of four evaluations of algorithms against external datasets identified during the targeted searches, selected the algorithm developed by Longworth et al. (2014) as being the best-performing tool in terms of accuracy across the spectrum of best and worst health states, involving relatively small mean absolute error (MAEs) and root mean squared error (RMSE) between observed and predicted values, and generalizability across country specific tariffs (127-130). The response mapping models used in Longworth et al. (2014) performed better than the regression models in terms of predictive ability. The Longworth et al. (2014) algorithm had the lowest MAE of any of the algorithms, which shows that it estimated the EQ-5D accurately. Additionally, it had one of the lower RMSE of the algorithms compared, again showing that the accuracy of the predictions is among the best of the models examined.

The Longworth algorithm was used to estimate EQ-5D-3L values with the Dolan et al (1997) tariff applied for UK-specific utilities (126),(131). The number of patients who were included in this mapping exercise and informed the modelled health state utility estimates is summarised by current response status in Table 51. Two approaches were explored to estimate utilities by health state based on the mapped EQ-5D data: 1) linear mixed effects models and 2) simple averages. The linear mixed effects models are better equipped to handle repeated measures (i.e., allows incorporation of all data collected over time and adjustment for covariates) and, thus was included in the model. Several models were explored, such as including treatment as a covariate, interaction terms, and random effects terms. The final model included tumour response as a three-level covariate (progressor/progression-free responder/progression-free non-responder), time in weeks, an interaction term between time and tumour response, and included a random intercept term to account for subject-specific effects (132).

The mapping analysis was conducted using the EMPOWER Lung-3 ITT population (any PD-L1, any histology population) rather than the restricted population for which

cemiplimab + chemotherapy has a UK marketing authorisation (i.e., PD-L1 ≥1%, any histology). This allowed use of all available data collected in EMPOWER-Lung 3 and a larger sample size, which was particularly important in the post-progression health state where observations were limited. QoL was assumed to be linked to disease progression, not the treatment received, therefore treatment-specific utilities were not estimated and therefore will not be impacted by PD-L1 status of the patients within the given health states. Table 46 summarises the utilities estimated from the linear fixed effects model and included in the CEM.

Figure 29 Mean EORTC QLQ-C30 response, global, June 2022 data cut

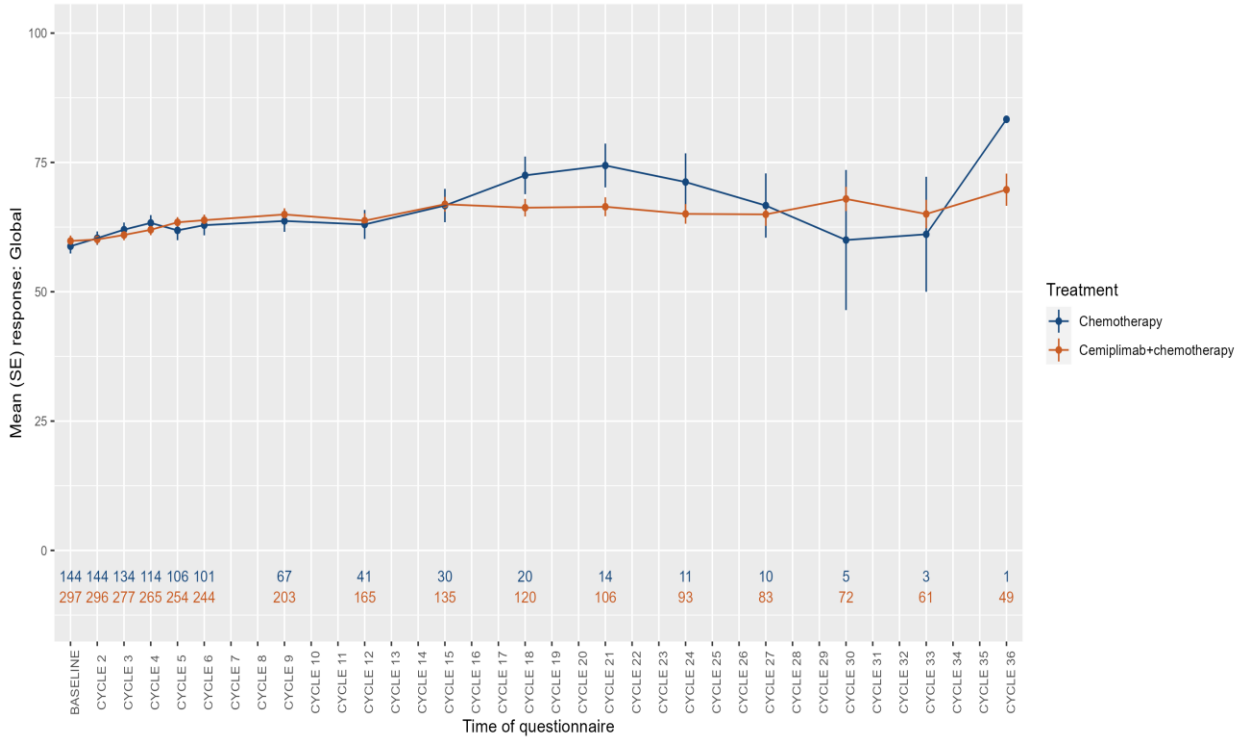


Table 45 EMPOWER-Lung 3 (part 2) EORTC QLQ-C30 observations over time, by current response status, June 2022 data cut

Tumor response	Visit															
	Baseline	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 9	Cycle 12	Cycle 15	Cycle 18	Cycle 21	Cycle 24	Cycle 27	Cycle 30	Cycle 33	Cycle 36
Progression-free	441	440	407	357	341	325	222	150	120	105	86	70	63	52	42	32
Progressed	0	0	4	22	19	20	48	56	45	35	34	34	30	25	22	18

Where a PRO assessment was provided but response wasn't available from the same date as PRO assessment, response was imputed using the last observation carried forward.

Table 46 EQ-5D-3L utility values included in the CEM, estimated using the Longworth et al. (2014) algorithm with UK tariff applied

Response status	Modelled average, mean (SE)
Progression-free	0.765 (0.005)
Progressed	0.723 (0.010)

SE, standard error.

B.3.4.4 Health related quality-of life data identified in the literature

An SLR was conducted in accordance with NICE methods and guidance to identify published sources of HRQoL data in NSCLC. A detailed explanation of the methods and results of the review is provided in Appendix H.

The original SLR was conducted in January 2020 with a global geographical scope, and a cut-off date of 2009. Subsequent updates were conducted in January 2021 and May 2022. A UK-only update was conducted in May 2024, and the results presented in this submission were restricted to studies with a UK patient component. Results of the SLR are presented in Table 47. Studies reporting HSUV data identified in the economic SLR are also presented in Table 47. Full details of the SLR methods are presented in Appendix H.

Table 47 Health related quality of life data identified in the literature

Study ID	Sources	Intervention/comparator	Utility mapping algorithm	Patient group (subgroup/strata)	Utility measure	Health State Utility Values (HSUVs)
NICE TA911 (95)	LIBRETTO-001 (133) (KEYNOTE-189) (16) Young et al. (2015) (134) NICE TA654 (135) NICE TA621 (136) NICE TA428 (35) NICE TA484 (137)	Intervention: Selpercatinib Comparator: Pembrolizumab plus Pemetrexed plus platinum containing chemotherapy and Pemetrexed plus platinum containing chemotherapy	Utility values included in the model were derived from values obtained from the LIBRETTO-001 trial, mapped to EQ-5D data using the algorithm presented in Young et al. (2015)	People with advanced rearranged during transfection (RET) fusion-positive, non-small cell lung cancer (NSCLC) who require systemic therapy	EQ-5D	**HSUVs (utility)** Progressed disease (PD); Mean: 0.678 (NICE TA654) **Disutility due to AEs** Diarrhoea; Mean: -0.047 (NICE TA621) Hypertension; Mean: -0.085 (NICE TA428) ECG QT prolonged; Mean: 0 (Assumption) Fatigue; Mean: -0.074 (NICE TA621) Decreased appetite; Mean: -0.085 (NICE TA428) Asthenia; Mean: -0.074 (NICE TA484) Vomiting; Mean: -0.085 (NICE TA428) Dyspnoea; Mean: -0.05 (NICE TA484) Alanine aminotransferase increased; Mean: -0.051 (NICE TA621) Aspartate aminotransferase increased; Mean: -0.051 (NICE TA621) Hyponatraemia; Mean: -0.085 (NICE TA428) Lymphopenia; Mean: -0.05 (NICE TA484) Pneumonia; Mean: -0.008 (NICE TA484) Thrombocytopenia; Mean: 0 (Assumption) Neutropenia; Mean: -0.09 (NICE TA428) Anaemia; Mean: -0.073 (NICE TA484)

Study ID	Sources	Intervention/comparator	Utility mapping algorithm	Patient group (subgroup/strata)	Utility measure	Health State Utility Values (HSUVs)
						Pleural effusion; Mean: -0.085 (NICE TA428) Febrile neutropenia; Mean: -0.09 (NICE TA428) Pneumonitis; Mean: -0.085 (NICE TA428) Nausea; Mean: -0.085 (NICE TA428) Hepatitis lab abnormalities; Mean: 0 (Assumption) Sepsis; Mean: 0 (Assumption) Acute kidney injury; Mean: 0 (Assumption) COPD; Mean: -0.085 (NICE TA428) UTI; Mean: 0 (Assumption) Peripheral neuropathy; Mean: -0.085 (NICE TA428) Decreased platelet count; Mean: 0 (Assumption) Decreased neutrophil count; Mean: 0 (Assumption) Severe skin reaction; Mean: 0 (Assumption) Proteinuria; Mean: 0 (Assumption)
NICE TA812 (2022) (125)	ARROW (138) Longworth et al (126) NICE TA654 (135) NICE TA713 (45) NICE TA428 (35) NICE TA261 (139)	Intervention: Pralsetinib Comparator: Platinum based chemotherapy with or without pemetrexed and Pembrolizumab combination with Pemetrexed plus Chemotherapy (docetaxel monotherapy) (docetaxel plus nintedanib)	A multinomial logistic regression approach as described by Longworth et al. was used.	Untreated RET fusion-positive advanced non-small-cell lung cancer (adult patients with RET fusion-positive advanced NSCLC not previously treated with a RET inhibitor.)	EQ-5D-3L mapped from EORTC QLQ-C32 (EORTC QLQ-C30)	**HSUVs (utility)** PF; Mean: 0.794 (NICE TA654) PD; Mean: 0.678 (NICE TA654) **Disutility due to AEs** Anaemia; Mean: -0.074 (NICE TA713) Asthenia; Mean: -0.074 (NICE TA713) Blood creatinine phosphokinase increased; Mean: 0 (Assumption) Decreased appetite; Mean: -0.085 (NICE TA428) Decreased neutrophils; Mean: 0 (Assumption)

Study ID	Sources	Intervention/comparator	Utility mapping algorithm	Patient group (subgroup/strata)	Utility measure	Health State Utility Values (HSUVs)
						Decreased white blood cell count; Mean: -0.05 (NICE TA713) Diarrhoea; Mean: -0.047 (NICE TA261) Disease progression; Mean: 0 (Assumption) Dyspnoea; Mean: -0.05 (NICE TA713) Fatigue; Mean: -0.074 (NICE TA261) Febrile neutropenia; Mean: -0.09 (NICE TA428) Hepatitis; Mean: 0 (Assumption) Hyperglycaemia; Mean: 0 (Assumption) Hypertension; Mean: -0.085 (NICE TA428) Hypocalcaemia; Mean: 0 (Assumption) Hyponatraemia; Mean: -0.085 (NICE TA428) Hypophosphataemia; Mean: 0 (Assumption) Increased ALT; Mean: 0 (Assumption) Increased AST; Mean: 0 (Assumption) Leukopenia; Mean: -0.0897 (NICE TA713) Lymphocyte count decreased; Mean: 0 (Assumption) Lymphopenia; Mean: -0.05 (NICE TA713) Malignant neoplasm progression; Mean: 0 (Assumption) Nausea; Mean: -0.085 (NICE TA428) Neutropenia; Mean: -0.09 (NICE TA428) Pain; Mean: 0 (Assumption)

Study ID	Sources	Intervention/comparator	Utility mapping algorithm	Patient group (subgroup/strata)	Utility measure	Health State Utility Values (HSUVs)
						Pleural effusion; Mean: -0.085 (NICE TA428) Pneumonia; Mean: -0.008 (NICE TA713) Pneumonitis; Mean: -0.085 (NICE TA428) Rash; Mean: 0 (Assumption) Sepsis; Mean: -0.09 (Assumed same as febrile neutropenia) Severe skin reactions; Mean: 0 (Assumption) Thrombocytopenia; Mean: 0 (Assumption) Urinary tract infection; Mean: -0.085 (NICE TA428) Vomiting; Mean: 0 (Assumption)
NICE TA770 (2022) (38)	KEYNOTE-407 (94) Khan et al., 2014 (140)	Intervention: KEYNOTE 407(94); Pembrolizumab, KEYNOTE 042(141); Pembrolizumab Comparator: KEYNOTE 407; Chemotherapy, KEYNOTE 402(141); Chemotherapy	N/A	Adults with untreated, metastatic, squamous non-small-cell lung cancer	EQ-5D	**HSUVs (utility) [Intervention arm]** Progressed disease [PD]; Mean: 0.58 (Khan et al., 2014) **HSUVs (utility) [Comparator arm]** Progressed disease [PD]; Mean: 0.62 (KEYNOTE-407)
NICE TA724 (2021) (96)	CheckMate-9LA (142)	Intervention: Nivolumab plus Ipilimumab plus limited platinum doublet chemotherapy Comparator: Ipilimumab plus standard chemotherapy	N/A	Adults with untreated stage IV or recurrent NSCLC that (with no known EGFR- or ALK-positive tumour mutations)	EQ-5D	**HSUVs (utility) [Nivolumab with ipilimumab and chemotherapy arm]** Utilities: > 52 weeks, Mean: 0.758 (CheckMate 9LA EQ-5D utilities analysis. 2020) Utilities: 27-52 weeks, Mean: 0.73 (CheckMate 9LA EQ-5D utilities analysis. 2020) Utilities: 5-26 weeks, Mean: 0.633 (CheckMate 9LA EQ-5D utilities analysis. 2020)

Study ID	Sources	Intervention/comparator	Utility mapping algorithm	Patient group (subgroup/strata)	Utility measure	Health State Utility Values (HSUVs)
						Utilities: ≤ 4 weeks, Mean: 0.409 (CheckMate 9LA EQ-5D utilities analysis. 2020) **Disutility of grade 3/4 adverse events** Anaemia, Mean: −0.125 (Lloyd et al., 2008) Neutropenia, Mean: −0.46 (Nafees et al., 2008) Fatigue, Mean: −0.41 (Nafees et al., 2008) Lipase increased, Mean: 0 (Assumption) Thrombocytopenia, Mean: −0.184 (Nafees et al., 2008) Neutrophil count decreased, Mean: −0.46 (Assumption) Platelet count decreased, Mean: 0 (Assumption) White blood cell count decreased, Mean: −0.46 (Nafees et al. 2008) Febrile neutropenia, Mean: −0.5 (Nafees et al., 2008)
NICE TA705 (2021) (40)	IMpower110 trial data (143)	Intervention atezolizumab Comparator Pembrolizumab	N/A (EQ-5D-3L used)	PD-L1 ≥50%	EQ-5D-3L	Redacted
NICE TA600 (2019) (97)	KEYNOTE-407 trial data (94)	Intervention Pembrolizumab + chemotherapy Comparator chemotherapy pembrolizumab	NA (EQ5D data)	Any PD-L1	EQ5D-3L	disutilities associated with AEs (values redacted)
NICE TA584 (2019) (43)	IMpower150 trial data (144) Huang, 2017 (145) Nafees et al., 2008 (146)	Intervention atezolizumab + carboplatin + paclitaxel + bevacizumab Comparator	N/A (EQ-5D-3L used)	PD-L1 <50%	EQ-5D-3L	**HSUVs (utility)** **Proximity to death approach base case – IMPOWER150**

Study ID	Sources	Intervention/comparator	Utility mapping algorithm	Patient group (subgroup/strata)	Utility measure	Health State Utility Values (HSUVs)
	Chouaid 2013 (43)	chemotherapy				≤ 5 weeks before death: 0.52 > 5 & ≤ 15 weeks before death: 0.59 > 15 & ≤ 30 weeks before death: 0.7 > 30 weeks before death: 0.73 **Pre and post progression scenario analysis – IMPOWER15** Pre progression: 0.71 Post progression: 0.69 **Pembrolizumab utilities proximity to death approach – Huang, 2017** ≤ 5 weeks before death: 0.537 > 5 & ≤ 15 weeks before death: 0.632 > 15 & ≤ 30 weeks before death: 0.726 > 30 weeks before death: 0.805 ≤ 5 weeks before death: 0.52 > 5 & ≤ 15 weeks before death: 0.59 > 15 & ≤ 30 weeks before death: 0.7 > 30 weeks before death: 0.73 **Scenario analysis – Nafees et al., 2008** Progression free: 0.66 (calculated based on regression coefficients) Progressed disease: 0.47 (calculated based on regression coefficients) **Scenario analysis – Chouaid et al. 2013** Progression free: 0.71 (calculated based on regression coefficients) Progressed disease: 0.67 (calculated based on regression coefficients)

Study ID	Sources	Intervention/comparator	Utility mapping algorithm	Patient group (subgroup/strata)	Utility measure	Health State Utility Values (HSUVs)
NICE TA557 (2019) (98)	KEYNOTE-189 trial data (147)	Intervention Pembrolizumab + chemotherapy Comparator chemotherapy	N/A (EQ5D used)	Any PD-L1	EQ-5D-3L	disutilities associated with AEs (values redacted)
NICE TA531 (2018) (39), SMC1239/17 (2017) (103)	KEYNOTE-024 trial data (148)	Intervention Pembrolizumab Comparator chemotherapy	N/A (EQ5D used)	PD-L1 ≥50%	EQ5D-3L	disutility per patient experiencing grade 3 to 5 AES: **pembrolizumab monotherapy:** 0.746 **chemotherapy:** 0.704 **pooled:** 0.719 disutility per patient not experiencing grade 3 to 5 AES: **pembrolizumab monotherapy:** 0.81 **chemotherapy:** 0.765 **pooled:** 0.793
SMC2573 (99)	LIBRETTO-001 trial cohort data TA654 (135)	Intervention: Selpercatinib Comparator: Pembrolizumab plus Pemetrexed plus platinum containing chemotherapy and Pemetrexed plus platinum containing chemotherapy	NR ('Utility values were based on EORTC QLQ-C30 data from the LIBRETTO-001 study, which were mapped onto the EQ-5D-3L UK value set.)	Adults with advanced RET fusion-positive NSCLC who have not been previously treated with a RET inhibitor and are treatment-naïve.	EQ-5D-3L	**HSUVs (utility)** Utility values were based on EORTC QLQ-C30 data from the LIBRETTO-001 study, which were mapped onto the EQ-5D-3L UK value set, and the details of mapping algorithm used were not provided. Scenario analysis was performed by considering alternative values from an appraisal for osimertinib in untreated EGFR mutation positive NSCLC
SMC2496 (100)	SMC2382 (149) SMC920/13 (150) SMC2294 (151) Ramalingam et al. 2020 FLAURA study (152)	Intervention: Pralsetinib Comparator: Platinum based chemotherapy with or	N/A (EQ-5D-3L taken from other HTAs)	Treatment-naïve patient with advanced RET-fusion positive NSCLC	EQ-5D-3L	**HSUVs (utility)** PF; Mean: 0.794 (Ramalingam et al. 2020 (FLAURA study))

Study ID	Sources	Intervention/comparator	Utility mapping algorithm	Patient group (subgroup/strata)	Utility measure	Health State Utility Values (HSUVs)
		without pemetrexed and Pembrolizumab combination with Pemetrexed plus Chemotherapy (docetaxel monotherapy) (docetaxel plus nintedanib)				
SMC 2379 (102)	IMpower110 trial data (143)	Intervention Atezolizumab Comparator pembrolizumab	NR	PD-L1 <50% TC3/IC3 (PD-L1 >50%)	EQ-5D-3L	Redacted
SMC2397 (101)	CheckMate9LA trial data (153)	Intervention nivolumab + ipilimumab + chemotherapy Comparator Chemotherapy pembrolizumab + chemotherapy	NR	PD-L1 <50%	EQ-5D-3L	Redacted
Jiang 2023 (104)	RCT data (IMpower150) (144) Ara et al, 2010 (154) Socinski et al., 2018 (155) Jassem et al., 2021 (156) van den Hout et al., 2006 (157) NICE TA911 (95) NICE TA876 (158) Nafees et al., 2008 (146)	Intervention: Atezolizumab Comparator: Chemotherapy (vinorelbine or gemcitabine)	N/A	Overall population	EQ-5D-3L	Health state utility; Utility for general people (age: 75, percent of male: 73%); Mean: 0.76 (Ara et.al, 2010) **HSUVs (utility) [Treatment arm]** Progression-free [PFS], base case analysis; Mean: 0.71 (Socinski et al., 2018) Progressed [PD], base case analysis; Mean: 0.69 (Socinski et al., 2018) PFS, scenario analysis; Mean: 0.76 (Jassem et al., 2021) PD, scenario analysis; Mean: 0.69 (Jassem et al., 2021) **HSUVs (disutility) [Treatment arm]** PFS, base case analysis; Mean: 0.11 (Socinski et al., 2018)

Study ID	Sources	Intervention/comparator	Utility mapping algorithm	Patient group (subgroup/strata)	Utility measure	Health State Utility Values (HSUVs)
						PD, base case analysis; Mean: 0.13 (Socinski et al., 2018) PFS, scenario analysis; Mean: 0.05 (Jassem et al., 2021) PD, scenario analysis; Mean: 0.11 (Jassem et al., 2021) **HSUVs (utility) [No treatment arm]** PFS; Mean: 0.62 (van den Hout et al., 2006) PD; Mean: 0.62 (van den Hout et al., 2006) **HSUVs (disutility) [No treatment arm]** PFS; Mean: 0.17 (van den Hout et al., 2006) PD; Mean: 0.17 (van den Hout et al., 2006) **Disutility due to Adverse Events [AEs]** Dyspnoea; Mean: 0.05 (NICE TA911) Anaemia; Mean: 0.08973 (NICE TA876) Neutropenia; Mean: 0.08973 (Nafees et al., 2008) Leukopenia; Mean: 0.08973 (NICE TA876) Nausea; Mean: 0.04802 (Nafees et al., 2008) Vomiting; Mean: 0.04802 (Nafees et al., 2008) Rash; Mean: 0.03 (Nafees et al., 2008)
Verma 2020 (105)	published literature via a rapid review (not otherwise specified)	Intervention Pembrolizumab Comparator	NR	PD-L1 expression unclear	NR	NR

Study ID	Sources	Intervention/comparator	Utility mapping algorithm	Patient group (subgroup/strata)	Utility measure	Health State Utility Values (HSUVs)
		Nivolumab				
Georgieva 2018 (108)	(Nafees, 2008) (146)	Intervention Pembrolizumab comparator chemotherapy	NR (pooled)	PD-L1 ≥50	EQ-5D	stable disease: NR[b] disease progression: NR[b]
Hu 2018 (b) (107)	published literature (not otherwise specified)	Intervention Pembrolizumab + chemotherapy Comparator chemotherapy	NR	Any PD-L1	NR	redacted
Tapan 2024 (159)	N/A	Intervention: Pembrolizumab + carboplatin-based therapy Comparator: Pembrolizumab + cisplatin-based therapy	N/A	Overall population	EQ-5D-3L	**HSUVs (utility) [Pembrolizumab + carboplatin-based therapy, OR Pembrolizumab + cisplatin-based therapy]** Overall patient population, base case weight; Mean: 0.516 Patients with brain metastases, base case weight; Mean: 0.433 Patients without brain metastases base case weight; Mean: 0.625
Bailey 2023 (160)	Adelphi NSCLC Disease Specific Programme	Intervention: 1L Setting	N/A	Patients with EGFR-WT/ALK-WT mNSCLC	EQ-5D utility index score (French 5L)	**HSUVs (utility)** 1L treatment, base case weight; Mean: 0.90
Huang 2019 (161)	KEYNOTE-024 (148)	Intervention: Pembrolizumab Comparator: IC chemotherapy	NR	Patients with PD-L1 ≥50%	EQ-5D-3L	**HSUVs (utility) [Pooled Pembrolizumab and Chemotherapy]** TOX, base case weight; Mean: 0.727 TWiST, base case weight; Mean: 0.803 REL, base case weight; Mean: 0.716

B.3.4.5 Impact of adverse events on quality of life

The model included QALY decrements associated with experiencing Grade 3+ adverse events (see Table 48). Disutilities were identified from targeted reviews of previously published economic evaluations and HTA submissions (i.e., TA724, TA359, TA772, TA515) (96, 162-164). The disutilities were applied to each treatment arm using the AE frequencies associated with each treatment included in the analysis (see Table 48). The model assumed an AE duration of 30 days to estimate the QALY decrements (i.e. one model cycle). The QALY decrements were applied as a one-off decrement in the first cycle of the analysis. The same assumption was accepted in NICE TA802 (108).

Table 48 Disutilities from published literature

Adverse event	Disutility	Source	Estimated QALY decrement[a]
Anaemia	-0.125	Lloyd et al. (2008) (165), assumed same as TA724 (96)	-0.010
Fatigue	-0.073	Reported as fatigue in Nafees et al. (2008)(146), referenced in TA724 (96)	-0.006
Neutropenia	-0.090	Reported as neutropenia in Nafees et al. (2008) (146), referenced in TA724 (96)	-0.007
Thrombocytopenia	-0.108	Tolley et al. (2013), based on TA359 (162)/TA772 (163)	-0.009

[a]Assuming a 30-day adverse event duration.
QALY, quality-adjusted life year.

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

As part of the economic SLR, searches were conducted to identify any healthcare resource utilisation (HRU) and costs in NSCLC. Details regarding the SLR and the HRU component are shown in Section B.3.1 and Appendix I.

B.3.5.1 Drug acquisition costs

Vial costs for all included interventions in the base case are summarised in Table 49. Drug acquisition and vial costs for all included interventions were sourced from the British National Formulary (BNF) 2023 (166) and the drugs and pharmaceutical electronic Market Information Tool (eMIT) National Database January 2023 to

December 2023 (167), which provides information about prices and usage for generic drugs and pharmaceutical products, and are summarised in Table 50. Where multiple vial sizes were available, the minimum cost per milligram was used. The model base case refers to the PD-L1 ≥1%, any histology population and the included interventions are cemiplimab + chemotherapy and pembrolizumab + chemotherapy (described in Section B.1.1). The costs for treatments included in the other subgroups are reported in Appendix I. Costs of concomitant medications for patients receiving doublet chemotherapy (e.g., steroids, paracetamol etc.) were not included as they are minimal and apply to all treatment arms.

Given the prevalence of weight and body surface area (BSA)-based dosing among the alternative chemotherapy regimens administered in combination with IOs, wastage (i.e., no vial sharing) was considered in base case analysis. The calculations were based on the normal distribution for BSA and log-normal distribution for weight, which was derived from the mean and standard deviation of weight or BSA for each gender in the EMPOWER-Lung 3 trial. The total drug dosage required for the specific weight or BSA distribution was calculated by multiplying weight or BSA distribution and the recommended drug dosage administration (mg/kg or mg/m^2) for the relevant percentiles of the distribution. The drug wastage was based on the difference between the total recommended dosage and the drug dosage received for each intervention assuming the most efficient use of available vials. When not assuming wastage in the model, average dose per administration was calculated using the average body weight of 72.79 kg and a body surface area (BSA) of 1.83 m^2 observed in the EMPOWER-Lung 3 trial (PD-L1 ≥1%, any histology population, see Table 27).

The distribution of chemotherapy regimens was assumed to the same for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. This ensures that any drug cost differences in the model are due to cost of the IOs rather than any differences due to heterogeneity in chemotherapy use across the clinical studies. UK clinical expert lung oncologists agreed that this was a reasonable assumption reflective of real-world practice. However, we consider this to be a conservative approach

because, as discussed in Section B.1.3.8, the use of cemiplimab may offer more flexibility of choice of chemotherapy backbone, including reduced need for pemetrexed-based chemotherapy (which does not currently have generic options) and lower starting AUC for carboplatin. For all the model arms the distribution of chemotherapy was based on the pooled EMPOWER-Lung 3 arms (see Table 52). This was due to limited reporting on the distribution of chemotherapy regimens from KEYNOTE-189 and 407. Feedback from UK clinical expert lung oncologists (see Section B.3.8.5) suggested that there was either no or extremely low use of cisplatin with either pemetrexed or paclitaxel currently in a UK setting. However, the inclusion of the small percentage of cisplatin-based regimens in the model based on EMPOWER-Lung 3 is unlikely to have a material effect on results given that both platinum therapies are generic and have the same administration cost.

Use of the chemotherapy distribution from EMPOWER-Lung 3 for both IOs potentially creates a disconnect between the TEAEs for pembrolizumab + chemotherapy used in the model (see Section B.3.3.4), as logically a significant proportion of the AEs observed in the pembrolizumab studies were a consequence of the distribution of chemotherapy regimens used. This is not anticipated to have a significant impact on the model as removal of AEs altogether from the model had little impact on results (see Section B.3.8.3).

Dosing for cemiplimab + chemotherapy was based on dosing in EMPOWER-Lung 3. For pembrolizumab + chemotherapy drug dosing for pembrolizumab was based on the KEYNOTE-407 and 189 studies while patients were receiving chemotherapy. Feedback from UK clinical expert lung oncologists (see Section B.3.8.5) was that patients often switch to the 400 mg once every six-week (Q6W) dosing of pembrolizumab if received as monotherapy after completion of initial chemotherapy. Therefore, patients were assumed to receive 200 mg pembrolizumab every 3 weeks (Q3W) as part of maintenance therapy with pemetrexed but 400 mg Q6W when receiving maintenance as monotherapy. UK clinical expert lung oncologists also explained that the Blueteq protocol for carboplatin in combination with pembrolizumab for people with squamous

disease specifies that patients “should be fit” to receive AUC 6 dose for carboplatin (consistent with the KEYNOTE-407 dosing, note KEYNOTE-189 implemented AUC 5 dosing for carboplatin) whereas patients receiving carboplatin in combination with cemiplimab are more likely to receive the AUC 5 dosing for carboplatin (EMPOWER-Lung 3 allowed for either AUC 5 or AUC 6 dosing) (168, 169). However, the model conservatively assumes that all patients in the model receive AUC 6 dosing, regardless of which IO they are treated with. Patients only receive carboplatin and cisplatin for a maximum of four cycles, in line with the EMPOWER-Lung 3, KEYNOTE-407 and 189 trial protocols. As AUC wasn’t available from EMPOWER-Lung 3, AUC 5 was assumed a maximum dose of 750 mg and AUC 6 was assumed a maximum dose of 900 mg (170).

Table 49: Reported reimbursement prices for all pre-progression treatments

Intervention	mg/ml per vial	Vial size (ml)	Total mg per vial	Cost per pack/vial	Source (171)
Cemiplimab	50 mg/ml	7 ml	350 mg	[redacted]	[redacted]% simple discount off the list price of £4,650.00. BNF 2023 (166)
Pemetrexed	25 mg/ml	4 ml	100 mg	£24.52	eMIT National Database January 2023 to December 2023 (167)
	25 mg/ml	20 ml	500 mg	£40.77	
	6 mg/ml	100 ml	600 mg	£118.56	
	7 mg/ml	100 ml	700 mg	£64.12	
	8 mg/ml	100 ml	750 mg	£72.51	
	8 mg/ml	100 ml	800 mg	£68.32	
	25 mg/ml	34 ml	850 mg	£52.04	
	9 mg/ml	100 ml	900 mg	£76.03	
	-	Powder	1000 mg	£11.04	
	11 mg/ml	100 ml	1100 mg	£889.65	
Paclitaxel	6 mg/ml	5 ml	30 mg	£3.88	
	6 mg/ml	17 ml	100 mg	£9.13	
	6 mg/ml	50 ml	300 mg	£24.43	
	6 mg/ml	25 ml	150 mg	£16.92	
Carboplatin	10 mg/ml	15 ml	150 mg	£20.22	
	10 mg/ml	60 ml	600 mg	£71.44	
	10 mg/ml	45 ml	450 mg	£48.09	
	10 mg/ml	5 ml	50 mg	£9.28	
Cisplatin	1 mg/ml	100 ml	100 mg	£29.27	
	1 mg/ml	10 ml	10 mg	£3.23	
	1 mg/ml	50 ml	50 mg	£27.98	
Nab-paclitaxel	5 mg/ml	20 ml	100 mg	£246.00	BNF 2023 (166)
Pembrolizumab	25 mg/ml	4 ml	100 mg	£2,630.00	

kg, kilogram; mg, milligram; ml, millilitre.

Table 50: Summary of drug doses/administration frequency

Intervention	Dosing regimen	Dose per administration	Unit	Comment
Cemiplimab	350 mg day 1 Q3W	350.00	mg	-
Paclitaxel	200 mg/m^2 Q3W	200.00	mg/m^2	-
Cisplatin	75 mg/m^2 Q3W,max 4 cycles	75.00	mg/m^2	-
Carboplatin (AUC5)	Assumed 750 mg flat dose, max 4 cycles	750.00	mg	Used in scenario analyses for cemiplimab + chemotherapy arm..
Carboplatin (AUC6)	Assumed 900 mg flat dose, max 4 cycles	900.00	mg	In combination with either cemiplimab or pembrolizumab

Intervention	Dosing regimen	Dose per administration	Unit	Comment
Pemetrexed	500 mg/m^2 Q3W	500.00	mg/m^2	-
Pembrolizumab (200 mg)	200 mg Q3W	200.00	mg	-
Pembrolizumab (400 mg)	400 mg Q6W	400.00	mg	-
Nab-paclitaxel	100 mg/m^2 (Days 1, 8, and 15) Q3W	100.00	mg/m^2	Available in the model but not included in the analyses.
Nivolumab (flat dose 240)	240 mg Q2W	240.00	mg	Post-progression only
Docetaxel	75 mg/m^2 Q3W	75.00	mg/m^2	Post-progression only
Gemcitabine	1250 mg/m^2 Q3W	1,250.00	mg/m^2	Post-progression only

AUC, area under curve; kg, kilogram; mg, milligram; m^2, meter squared; ml, millilitre; QW2, every 2 weeks; Q3W, every 3 weeks; Q6W, every six weeks.

Table 51: Drug dosages and acquisition costs for cemiplimab + chemotherapy and comparators

Intervention	Treatment arm	Dosage	Cost per administration[a] (£)	Cost per NMA cycle, including wastage(£)
Cemiplimab + chemotherapy	Cemiplimab	350 mg, Day 1 Q3W	4,650.00	6,739.73
	Paclitaxel	200 mg/m^2, Day 1 Q3W	33.59	48.68
	Carboplatin	900 mg, Day 1 Q3W	96.18	139.40
	Cisplatin	75 mg/m^2, Day 1 Q3W	46.02	66.70
	Pemetrexed	500 mg/m^2, Day 1 Q3W	13.14	19.05
Pembrolizumab + chemotherapy	Pembrolizumab	200 mg, Day 1 Q3W	5,260.00	7,623.87
	Pembrolizumab	400 mg, Day 1 Q6W	10,520.00	7,623.87
	Paclitaxel	200 mg/m^2, Day 1 Q3W	33.59	48.68
	Carboplatin	900 mg, Day 1 Q3W	96.18	139.40
	Cisplatin	75 mg/m^2, Day 1 Q3W	46.02	66.70
	Pemetrexed	500 mg/m^2, Day 1 Q3W	13.14	19.05

Costs per administration are estimated using patient characteristics for any histology and ≥1% PD-L1 level; a) cost per administration based on wastage (i.e., no vial sharing) for weight or BSA based dosing.
kg, kilogram; mg, milligram; Q3W, every 3 weeks; Q6W, every 6 weeks.

Table 52: Percentage of usage of each chemotherapy regimen for cemiplimab + chemotherapy and pembrolizumab +chemotherapy

Intervention	Chemotherapy regimens	Proportion of patients receiving each chemotherapy regimen(172)
Cemiplimab + chemotherapy or pembrolizumab + chemotherapy	Pemetrexed + cisplatin	8%
	Pemetrexed + carboplatin	35%
	Paclitaxel + cisplatin	5%
	Paclitaxel + carboplatin	51%
	Pemetrexed maintenance	11%

[a]Proportion same as pemetrexed + cisplatin EMPOWER-Lung 3; [b]Proportion same as pemetrexed + carboplatin EMPOWER-Lung 3; [c]Sum of proportion of paclitaxel combinations EMPOWER-Lung 3; d) anticipating the distribution of chemotherapies to be similar between cemiplimab and pembrolizumab combinations in the real world and thus, assumed to be zero. WA, weighted average.

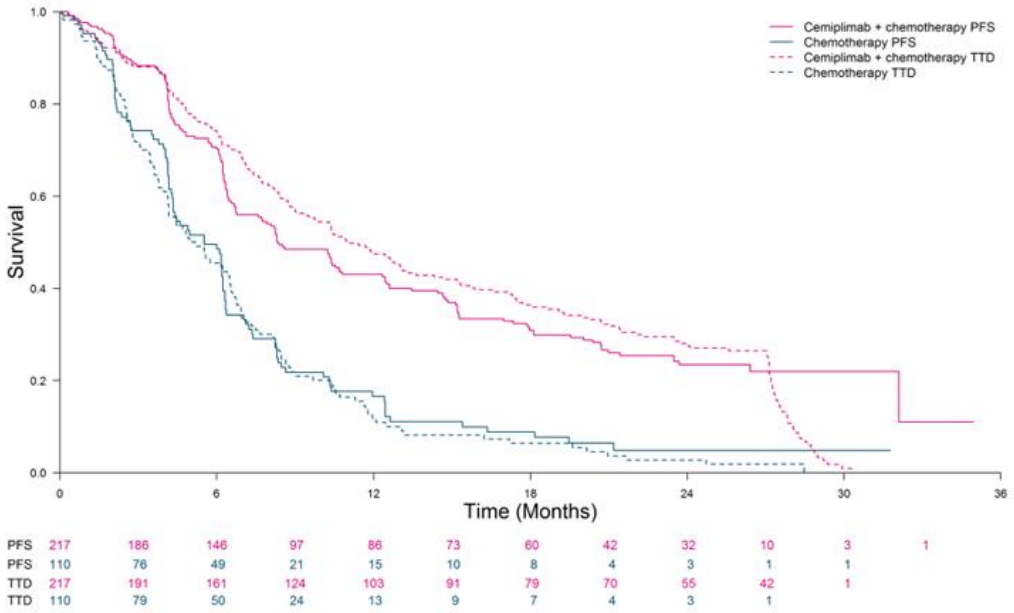
Time on treatment

Time on treatment (ToT or else Time-to-Treatment Discontinuation, TTD) and PFS from EMPOWER-Lung 3 are available in Figure 30. The EMPOWER-Lung 3 protocol allowed patients to continue treatment beyond the initial RECIST 1.1-defined progressive disease if the investigator perceived the patient to be experiencing clinical benefit, the patient had not completed the 108-week treatment period and the patient met the following criteria:

- Investigator assessed no rapid disease progression,
- Patient continued to meet all other study eligibility criteria,
- Patient was tolerant of cemiplimab and had a stable performance status,
- Treatment beyond progression would not delay an imminent intervention to prevent serious complications of disease progression.

However, the MHRA label for cemiplimab specifies that cemiplimab treatment “may be continued until disease progression or unacceptable toxicity”. Based on the MHRA label and the opinion of UK clinical expert lung oncologists (see Section B.3.8.5), it is not anticipated that treatment will continue beyond progression in clinical practice, as it did in the clinical trial for some patients. Note for the chemotherapy arm, both TTD and PFS were aligned in EMPOWER-Lung 3 as shown in Figure 30. In the base case, ToT in the model was assumed equal to PFS for cemiplimab + chemotherapy, and pembrolizumab + chemotherapy.

Figure 30 PFS and TTD for cemiplimab + chemotherapy and chemotherapy from EMPOWER-Lung 3 (June 2022 DCO) in the PD-L1 ≥1%, any histology population



PFS, progression-free survival; TTD, time to treatment discontinuation.

As an alternative to assuming ToT was equal to PFS, the model was programmed to allow users to apply a HR to the PFS curve for each treatment to model a separate ToT curve (see Table 53). At the advisory board meeting by Regeneron (see Section B.3.8.5), advisors were cautious about concluding the discrepancies between cemiplimab + chemotherapy and pembrolizumab + chemotherapy. They suggested these differences might be due to IO experience bias or reporting variations between trials. For EMPOWER-Lung 3, the HR was estimated by means of a Cox model. Note the underlying assumption of independence of groups is violated, as patients are included in each 'group' defined by the outcome (i.e., PFS and TTD), so the HR should be interpreted with caution. For pembrolizumab + chemotherapy, a HR was estimated from the median PFS and ToT reported in the KEYNOTE studies where a publication reported both median PFS and ToT from the same data cut. KEYNOTE-407 (14.3 months of follow-up) reported a median PFS of 8 months and a median ToT of 7.1 months. KEYNOTE-189 (31 months of follow-up) reported a median PFS of 9 months and a median ToT of 7.2 months. Hazards were estimated from the medians using an exponential distribution and hazard ratios were calculated and weighted by split of squamous and non-squamous patients in EMPOWER-Lung 3. This was evaluated as a scenario analysis.

Table 53: Hazard ratios available to estimate time on treatment in the model

Treatment	Estimated hazard ratio	Source
Cemiplimab + chemotherapy	1.17	EMPOWER-Lung 3(86)
Pembrolizumab + chemotherapy	0.84	KEYNOTE-407(173) and KEYNOTE-189(174), weighted by split of squamous and non-squamous in EMPOWER-Lung 3(86)

Maximum treatment duration

In addition to the methods described above, the CEM had the functionality to apply a maximum treatment duration for each treatment in the model. The inclusion of maximum treatment duration functions was considered on a case-by-case basis for each treatment option in the model to ensure flexibility to stop individual components of combination therapies where required.

The model's maximum treatment duration for cemiplimab + chemotherapy was 24 months for cemiplimab, up to 4 cycles of chemotherapy, and pemetrexed maintenance for non-squamous patients until progression in alignment with the 108 week stopping rule in EMPOWER Lung-3 and the NICE recommendations for pembrolizumab + chemotherapy (TA683 and TA770) (38, 44). For pembrolizumab + chemotherapy, the maximum duration was 24 months for pembrolizumab, up to 4 cycles of chemotherapy, and pemetrexed maintenance until progression, in alignment with the registrational KEYNOTE studies and the NICE recommendations for pembrolizumab + chemotherapy (TA683 and TA770) (38, 44).

These stopping rules were validated by UK clinical experts (see Section B.3.8.5) who agreed that treatment beyond progression was not anticipated in clinical practice and that a 2-year stopping rule for IO is appropriate based on the current evidence base.

B.3.5.2 Administration costs

Relevant administration unit costs were sourced from the NHS Reference costs 2022/23 (see Table 54) (175, 176). The administration cost was applied to each treatment option in the model based on its administration frequency (see Table 51) and the duration of chair time for delivering the regimen according to published NHS protocols (177). As IO is administered prior to chemotherapy and concomitantly with

chemotherapy premedication, IO was assumed not to add additional chair time to combination regimens, an assumption confirmed by UK clinical expert lung oncologists. The costs per administration are summarised in Table 54.

Table 54: Costs of IV administration

Activity	Unit cost (£)	Source
IO in combination with initial chemotherapy (platinum plus pemetrexed, or platinum plus paclitaxel)	360.68	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance. NHS Reference costs 2022/23, SB14Z (outpatient, more than 180 minutes) (175, 176)
IO in combination with pemetrexed as maintenance	276.57	Deliver more Complex Parenteral Chemotherapy at First Attendance. NHS Reference costs 2022/23, SB13Z (outpatient, between 60 and 180 minutes) (175, 176)
IO monotherapy as maintenance	217.20	Deliver Simple Parenteral Chemotherapy at First Attendance. NHS Reference costs 2022/23, SB12Z (outpatient, up to 60 minutes) (175, 176)
Pemetrexed monotherapy as maintenance	217.20	Deliver Simple Parenteral Chemotherapy at First Attendance. NHS Reference costs 2022/23, SB12Z (outpatient, up to 60 minutes) (175, 176)

IO, immunotherapy, IV, intravenous; NHS, National Health Service.

B.3.5.3 Subsequent treatment

Following progression on first-line treatment, subsequent therapy costs were applied for patients in the post-progression health state (see Table 55). The cost of subsequent therapies for each treatment arm was calculated as a weighted average cost considering the distribution of subsequent treatments received in second line and beyond, treatment costs per cycle (drug acquisition and administration), and treatment duration. In the model trace, the estimated cost is then divided by the total time in post-progression, which is then multiplied by the proportion of time in post-progression at each cycle. In essence, a one-time cost for subsequent therapy is applied based on the proportion of the starting cohort receiving subsequent therapy, distribution of subsequent therapies received, and the duration of subsequent therapy, but the costs are spread across the post-progression health state to better reflect discounting.

Subsequent therapies received by ≥1% of patients in either the cemiplimab + chemotherapy or chemotherapy arm of the EMPOWER-Lung 3 trial were included in the model. Note in the chemotherapy arm, two patients (1.3%) received subsequent therapy with sintilimab. As this therapy is not licensed in Europe the patients were redistributed across pembrolizumab, nivolumab and atezolizumab. The distribution of subsequent therapies were not anticipated to vary significantly across PD-L1

subgroups, thus are based on the any PD-L1, any histology population (i.e. ITT) from EMPOWER-Lung 3. The uptake of subsequent therapies was lower than anticipated, likely due to the relatively short follow-up in post-progression in the EMPOWER-Lung 3 trial at the data cut-off date. For pembrolizumab + chemotherapy, the same post-progression distribution of subsequent therapy as cemiplimab + chemotherapy was assumed. We acknowledge that subsequent IO following failure of initial IO isn't funded by the NHS. However, the proportions of patients who received subsequent IO treatment in the EMPOWER-Lung 3 cemiplimab + chemo arm are so low that the inclusion of these costs is expected to have minimal impact on results.

Information to inform the duration of subsequent therapy was not collected in EMPOWER-Lung 3, thus duration of subsequent therapy was based on estimates reported in Insinga et al (2021) (117). The duration is based on the duration of 2nd line therapy included for the pembrolizumab + chemotherapy arm of KEYNOTE-189 of 256 days for anti-PD1/PD-L1 therapies (rounded to 8 months) and 109 days for chemotherapies (rounded to 4 months).

Drug acquisition and vial costs for all included post-progression interventions were sourced from the BNF 2023 and eMIT 2023 (166, 167). The same approach applied for the estimation of pre-progression costs in the base case was applied for post-progression costs (i.e. including wastage costs). Drug dosages and acquisition costs for all included interventions are summarised in Table 57.

For all subsequent therapies, a cost per administration was also applied, based on the NHS Reference costs 2022/23 (see Table 54) (175, 176). In the absence of any information, all treatments were assumed to be administered as monotherapies so administration code SB12Z was applied. The distribution of subsequent therapies included in the analysis was validated by UK clinical experts lung oncologists as part of the advisory board follow-up interviews (see Section B.3.8.5).

A scenario analysis was conducted where subsequent treatment distributions sourced from EMPOWER-Lung 3 were reweighted to align with the overall distribution for IO and other systemic therapies observed in KEYNOTE-189 study (see Section B.3.8.3).

Table 55: Distribution of post-progression subsequent treatment

Post-progression treatment[a] ↓	Initial (pre-progression) treatment: Cemiplimab + chemotherapy	Initial (pre-progression) treatment: Pembrolizumab + chemotherapy[b]
Immunotherapies		
Pembrolizumab	0.6%	0.6%
Nivolumab	0.0%	0.0%
Atezolizumab	0.3%	0.3%
Chemotherapies		
Docetaxel	4.5%	4.5%
Carboplatin	5.4%	5.4%
Cisplatin	1.9%	1.9%
Gemcitabine	3.5%	3.5%
Paclitaxel	3.2%	3.2%
Pemetrexed	1.9%	1.9%

[a]Subsequent therapies received by ≥1% of patients in either the cemiplimab + chemotherapy or chemotherapy arm of the EMPOWER-Lung 3 trial were included in the model; [b]Assumed same as cemiplimab + chemotherapy.

Table 56: Weighted average costs for all post-progression treatments

Intervention	mg/ml per vial	Vial size (ml)	Total mg per vial	Cost per pack/vial (£)	Source(166, 167, 171)
Immunotherapies					
Pembrolizumab	25 mg/ml	4 ml	100 mg	£2,630.00	BNF 2023(166)
Nivolumab	10 mg/ml	24.0 mL	240 mg	£2,633.00	
	10 mg/ml	12.0 mL	120 mg	£1,317.00	
	10 mg/ml	10.0 mL	100 mg	£1,097.00	
	10 mg/ml	4.0 mL	40 mg	£439.00	
Atezolizumab	125 mg/ml	15 mg/ml	1875 mg	£5,949.52	SC treatment (price per mg assumed same other atezolizumab formulations)
	60 mg/ml	20 ml	1200 mg	£3,807.69	BNF 2023(166)
	60 mg/ml	14 ml	840 mg	£2,665.38	
Chemotherapies					
Docetaxel	20 mg/ml	8 ml	160 mg	£18.01	eMIT National Database January 2023 to December 2023(167)
	20 mg/ml	1 ml	20 mg	£3.67	
	20 mg/ml	4 ml	80 mg	£9.07	
Carboplatin	10 mg/ml	15 ml	150 mg	£20.22	
	10 mg/ml	60 ml	600 mg	£71.44	
	10 mg/ml	45 ml	450 mg	£48.09	
	10 mg/ml	5 ml	50 mg	£9.28	
Cisplatin	1 mg/ml	100 ml	100 mg	£29.27	
	1 mg/ml	10 ml	10 mg	£3.23	
	1 mg/ml	50 ml	50 mg	£27.98	
Gemcitabine	-	Powder	200 mg	£3.51	
	38 mg/ml	5 ml	201 mg	£4.10	
	38 mg/ml	26 ml	999 mg	£10.08	
	-	Powder	1000 mg	£9.86	
	10 mg/ml	120 ml	1200 mg	£35.24	

Intervention	mg/ml per vial	Vial size (ml)	Total mg per vial	Cost per pack/vial (£)	Source(166, 167, 171)
	10 mg/ml	130 ml	1300 mg	£43.20	
	10 mg/ml	140 ml	1400 mg	£36.40	
	10 mg/ml	160 ml	1600 mg	£38.28	
	10 mg/ml	180 ml	1800 mg	£41.32	
	2g	20 ml	2000 mg	£17.97	
Paclitaxel	6 mg/ml	5 ml	30 mg	£3.88	
	6 mg/ml	17 ml	100 mg	£9.13	
	6 mg/ml	50 ml	300 mg	£24.43	
	6 mg/ml	25 ml	150 mg	£16.92	
Pemetrexed	25 mg/ml	4 ml	100 mg	£24.52	
	25 mg/ml	20 ml	500 mg	£40.77	
	6 mg/ml	100 ml	600 mg	£118.56	
	7 mg/ml	100 ml	700 mg	£64.12	
	8 mg/ml	100 ml	750 mg	£72.51	
	8 mg/ml	100 ml	800 mg	£68.32	
	25 mg/ml	34 ml	850 mg	£52.04	
	9 mg/ml	100 ml	900 mg	£76.03	
	-	Powder	1000 mg	£11.04	
	11 mg/ml	100 ml	1100 mg	£889.65	

mg, milligram; ml, milliliter.

Table 57: Drug dosages and acquisition costs for post-progression treatments

Intervention	Dosage	Duration(117) (months)	Cost per administration[a] (£)	Cost per monthly cycle (£)
Immunotherapies				
Pembrolizumab	200 mg, Day 1 Q3W	8	5,260.00	7,623.87
Nivolumab	240mg, Day 1 Q2W	8	2,632.80	5,723.99
Atezolizumab	1200 mg, Day 1 Q3W	8	3,807.69	5,518.88
Chemotherapies				
Docetaxel	75 mg/m^2, Day 1 Q3W	4	18.03	26.13
Carboplatin	750 mg, Day 1 Q3W	4	80.15	116.17
Cisplatin	75 mg/m^2, Day 1 Q3W	4	46.02	66.70
Gemcitabine	1250 mg/m^2, Day 1 Q3W	4	26.60	38.56
Paclitaxel	200 mg/m^2, Day 1 Q3W	4	33.59	48.68
Pemetrexed	500 mg/m^2, Day 1 Q3W	4	13.14	19.05

Costs per administration are estimated using patient characteristics for any histology and ≥1% PD-L1 level; a) cost per administration based on wastage (i.e., no vial sharing) for weight or BSA based dosing.
kg, kilogram; mg, milligram; Q2W, once every 2 weeks; Q3W, once every 3 weeks.

B.3.5.4 Routine care

Healthcare resources and associated costs for routine disease management in the pre- and post-progression health states were also included in the model. The frequency of healthcare resource use and unit costs of the activity in the pre- and post-progression health states are reported in Table 58 and Table 59. Healthcare resource use was sourced from NICE TA531 (39) which evaluated the use of pembrolizumab monotherapy for treating untreated PD-L1-positive metastatic NSCLC patients. This informed routine disease management in the UK. Unit costs were sourced from the NHS Reference Costs, PSSRU Unit Costs, and NICE TA531 (39, 175, 176). The frequency of healthcare resource use in the pre- and post-progression health states was assumed to be identical for all therapies. The healthcare resource use and associated costs included in the analysis was validated by UK clinical experts as part of advisory board follow-up interviews (see Section B.3.8.5).

Table 58: Routine disease management, pre- and post-progression health state

Resource	Pre-progression, frequency per month		Post-progression, frequency per month		Source
	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy	
Outpatient visit	0.80	0.80	0.66	0.66	NICE TA531 (39)
Chest radiography	0.57	0.57	0.54	0.54	
CT scan (Chest)	0.05	0.05	0.02	0.02	
CT scan (Other)	0.03	0.03	0.04	0.04	
ECG	0.09	0.09	0.07	0.07	
Community nurse visit	0.73	0.73	0.73	0.73	
Clinical nurse specialist	1.00	1.00	1.00	1.00	
GP surgery	1.00	1.00	-	-	
GP home visit	-	-	2.17	2.17	
Therapist visit	-	-	2.17	2.17	

CT, computerized tomography; ECG, electrocardiogram; GP, general practitioner; NICE, National Institute of Health and Care Excellence; TA, Technology appraisal.

Table 59 Unit costs of HCRU

Resource	Unit cost (£)	Source (based on TA531(39))
Outpatient visit	145.96	NHS Reference costs 2022/23-WF01A-800, Non-Admitted Face-to-Face Attendance Follow-up.(175, 176)
Chest radiography	31.94	NICE TA531 (TA199, p.328 - £24.04 in 2009), inflated to 2023 using NSHCII pay and prices index.(175, 176)
CT scan (Chest)	146.55	NHS Reference costs 2022/23- RD24Z, Computerised Tomography Scan of Two Areas, with Contrast (Total HRGs).(175, 176)
CT scan (Other)	166.51	NHS Reference costs 2022/23- RD26Z, Computerised Tomography Scan of Two Areas, with Contrast (Total HRGs).(175, 176)
ECG	176.98	NHS Reference costs 2022/23- EY51Z clinical oncology outpatient, Electrocardiogram Monitoring or Stress Testing.(175, 176)
Community nurse visit	76.00	PSSRU 2023, p.62. Cost per working hour Band 8a.(176)
Clinical nurse specialist	89.00	PSSRU 2023, p.62. Cost per working hour Band 8b.(176)
GP surgery	55.00	PSSRU 2023, p.65: GP cost including direct care staff costs and with qualifications (10 minutes per surgery consultation).(176)
GP home visit	103.23	PSSRU 2023: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel (TA531), assumed 11.4 minutes of patient contact and 12 minutes of GMS activity.(176)
Therapist visit	52.00	PSSRU 2023, p.78: Cost per hour for community occupational therapist (including qualifications).(176)

CT, computerized tomography; ECG, electrocardiogram; HCRU, health care resource use; GP, general practitioner; NHSCII, National Health Service Cost Inflation Index; NICE, National Institute of Health and Care Excellence; PSSRU, Personal Social Services Research Unit; TA, Technology appraisal.

B.3.5.5 End-of-life care

A one-off cost for end-of-life care was applied upon transition to the death health state. The one-off cost was estimated from the distribution of patients and the respective unit costs for patients receiving home, hospital and hospice care respectively, sourced from the PSSRU costs 2023 (176), NHS Reference Costs (175), and assumptions taken from NICE TA531 (39) (see Table 60).

Table 60: Terminal care costs

Activity	Percentage of patients	Unit cost (£)	Number of services	Source (based on TA531(39))
Community nurse visit	27%	76.00 per hour	28.0	PSSRU 2023, p.62. Cost per working hour Band 8a (176)
GP home visit		103.23 per visit	7.0	PSSRU 2023: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel (TA531), assumed 11.4 minutes of patient contact and 12 minutes of general medical service activity (176)
Macmillan nurse		50.69 per hour	50.0	Unit cost assumed to be 66.7% of community nurse (assumption aligned with TA531), HCRU taken from NICE TA531 (39)
Drugs and equipment		661.17 per patient	1.0	NICE TA531 2015/2016 price of £553 per patient, inflated to 2023 using NSHCII pay and prices index (175, 176)
Terminal care in hospital	56%	5,292.82 per episode	1.0	Average of NHS Reference Costs 2022/23, DZ17L (Respiratory Neoplasms with Multiple Interventions, with CC Score 10+), DZ17P (Respiratory Neoplasms with Single Intervention, with CC Score 10+) and DZ17T (Respiratory Neoplasms without Interventions, with CC Score 8-12), non-elective long stay (175, 176)
Terminal care in hospice	17%	6,616.02 per episode	1.0	Assumed 25% increase on hospital inpatient care in line with assumption in NICE TA531 (39)
Total terminal care cost of £5721.22				

HCRU, health care resource use; NHS, National Health Services, NHSCII, National Health Service Cost Inflation Index; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit, TA, technology appraisal.

B.3.5.6 Cost of treating adverse events

Hospitalisation costs associated with the treatment of Grade 3+ AEs were sourced from the literature and included in the model (Table 61). Unit costs were derived from the NHS reference costs (175) (non-elective short stay, non-elective long-stay and day case) based on NHS Reference codes reported in NICE, TA347, TA802 and

HRG code: SA12G-K (5, 35, 39, 46, 178). The total cost of adverse events was applied as a one-off cost in the first cycle of the model.

The frequency of adverse event occurrence by treatment included in the model is outlined in Table 43**.**

Table 61: Adverse event costs

Adverse event	Unit cost (£)	Source
Anaemia	1,998.31	NHS Reference Costs 2022/23; HRG code: SA01G-K (code used in TA347), assumes non-elective long-stay, non-elective short stay and day case (46)
Fatigue	1,998.31	Assumed the same as anaemia (as in TA347) (46)
Neutropenia	584.77	NHS Reference Costs 2022/23 (175), HRG code: WJ11Z (updated from code WA02W [no longer reported, "disorders of immunity without HIV/AIDS with complicating condition"] used in Brown et al. 2013, accepted in TA802) (5, 178) assumes non-elective long-stay, non-elective short stay and day case.
Thrombocytopenia	1,127.02	NHS Reference Costs 2022/23 (175), HRG code: SA12G-K (Thrombocytopenia with CC Score 0-8+).

NHS, National Health Service, NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

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

The results presented in Section B.3.7.1 are for the base case cost-effectiveness analysis for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy and chemotherapy in the PD-L1 ≥1%, any histology. The main assumptions taken in the base case are summarised in Table 62. The base assumptions were chosen to reflect the NICE reference case as closely as possible. The clinical data sources used in the model are summarised in Table 63.

Parameters values applied in the base case, their distributions and variance are reported in Appendix R.

Table 62: Base case cost-effectiveness analysis settings, PD-L1 ≥1% and any histology

Parameter	Value	Justification
Population	PD-L1 ≥1%, any histology	Aligned with MHRA license for cemiplimab + chemotherapy.
Patient characteristics	Median age 62 years old, mean weight 72.8 kg, BSA 1.83 m^2	Aligned with target population in EMPOWER-Lung 3.
Progression-free survival (reference curve = chemotherapy)	*Chemotherapy:* Log-logistic distribution fit to progression-free survival data from EMPOWER-Lung 3. *Cemiplimab + chemotherapy, pembrolizumab + chemotherapy:* application of treatment effects	Log-logistic was the favoured NMA model, lowest AIC/BIC, best fit to hazards, and offered clinically plausible survival projections which were validated by UK clinical expert lung oncologists.

Parameter	Value	Justification
	from the two-step NMA to the shape and scale parameters for the reference curve	
Overall survival for (reference curve = chemotherapy)	*Chemotherapy:* Log-logistic distribution fit to overall survival data from EMPOWER-Lung 3 *Cemiplimab + chemotherapy, pembrolizumab + chemotherapy:* application of treatment effects from the two-step NMA to the shape and scale parameters for the reference curve	Log-logistic was the favoured NMA model, AIC/BIC similar to best fitting model, and offered clinically plausible survival projections which were validated by UK clinical expert lung oncologists.
Treatment waning	PFS and OS Hazards for cemiplimab + chemotherapy and pembrolizumab + chemotherapy assumed equal to chemotherapy at five years.	Experts interviewed in the advisory board meeting (see Section B.3.8.5) expect treatment effects to continue up to five years (i.e., up to three years beyond end of treatment) for IO. Continuation of treatment effect is supported by five-year follow-up from KEYNOTE 407 and 189, which support continued treatment effect after 24 months.
Treatment duration	Assumed equal to PFS for all interventions	Assumed equal to PFS for cemiplimab + chemotherapy as treatment past progression (as allowed by the EMPOWER-Lung 3 protocol) is not anticipated in clinical practice. Same assumption applied for pembrolizumab + chemotherapy.
Treatment stopping rules	*Chemotherapy:* max of 4 cycles, non-squamous patients can receive pemetrexed maintenance therapy until progression. *Cemiplimab + chemotherapy:* 24 months for cemiplimab, max of 4 cycles of chemotherapy and non-squamous patients can receive pemetrexed maintenance therapy until progression. *Pembrolizumab + chemotherapy:* 24 months for pembrolizumab, max of 4 cycles of chemotherapy and pemetrexed maintenance therapy until progression.	Aligned with EMPOWER-Lung 3 for cemiplimab + chemotherapy and anticipated NICE recommendation and aligned with NICE recommendation for pembrolizumab + chemotherapy.
Utility values	Modelled utility values from EORTC-QLQ-C30 from EMPOWER-Lung 3 ITT mapped to the EQ-5D-3L, using Longworth et al (2014) mapping algorithm and UK tariff (Dolan et al. 1997)	Utilises data from the full ITT population.
Drug costs	Drug costs for cemiplimab include the current PAS discount. Other drug costs are based on the UK list prices (or price paid by the NHS, where available).	As per NICE submission guidance notes.
Health care resource utilisation	Based on TA531	Resource use previously accepted by the NICE committee.

AIC, Akaike information criterion; BIC, Bayesian information criterion; BSA, body surface area; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; ITT, intention to treat; MHRA, Medicines

and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TA, technology appraisal.

Table 63 Summary of model clinical inputs

Clinical evidence and source	Brief description	Use in the model
EMPOWER Lung-3	A double-blind, placebo-controlled phase 3 study, investigated cemiplimab plus chemotherapy versus placebo plus chemotherapy in patients with advanced NSCLC without *EGFR*, *ALK*, or *ROS1* aberrations, with either squamous or non-squamous histology, irrespective of programmed death-ligand 1 levels	• Source of efficacy data • Source of safety data • Source of utility data • Chemotherapy arm used as the reference arm in the model • ToT estimation • Maximum treatment duration • Average body weight for drug acquisition costs
KEYNOTE-189	A Randomized, Double-Blind, Phase III Study of Platinum + Pemetrexed Chemotherapy With or Without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects	• ToT estimation • Evaluated as the reference arm as a scenario analysis • Drug dosing for pembrolizumab
KEYNOTE- 407	A Randomized, Double-Blind, Phase III Study of Carboplatin-Paclitaxel/Nab-Paclitaxel Chemotherapy With or Without Pembrolizumab (MK-3475) in First Line Metastatic Squamous Non-small Cell Lung Cancer Subjects	• ToT estimation • Evaluated as the reference arm as a scenario analysis • Drug dosing for pembrolizumab

NSCLC, non-small cell lung cancer, ToT, time on treatment

B.3.7 Base-case results

Base-case results from the cost-utility analysis comparing cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in the PD-L1 ≥1%, any histology population (i.e., MHRA label population) are presented in Section B.3.7.1.

As discussed in Section B.2.9, while results from the NMA informing the cost-utility analysis typically directionally favour cemiplimab + chemotherapy (e.g., PFS/OS), Regeneron acknowledges the meaningful uncertainty associated with this analysis, largely due to inherent limitations in the available evidence base. Regeneron therefore considers a cost comparison analysis approach, assuming the same clinical outcomes for cemiplimab + chemotherapy and pembrolizumab + chemotherapy, to be highly pertinent to committee decision making. Results from this cost comparison analysis are presented in Section B.3.7.2 as an 'alternative base case'.

B.3.7.1 Cost-utility analysis

From a UK NHS and personal social services (PSS) perspective, and at a PAS price of [redacted] per 350 mg vial, cemiplimab + chemotherapy was found to be a dominant treatment option versus pembrolizumab + chemotherapy for NSCLC patients with PD-L1 ≥1%, and any histology. This was based on an incremental cost saving of [redacted], and an incremental QALY gain of [redacted] versus pembrolizumab + chemotherapy. Base case results are presented in Table 64 and disaggregated results for the base case analysis are presented in Table 65.

Table 64: Incremental results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy (discounted), PD-L1 ≥1% and any histology

	Total			Incremental			ICER (£)
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	
Cemiplimab +chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	126,144	2.93	2.15	-	-	-	-

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; pembro + chemo, pembrolizumab + chemotherapy.

Table 65: Disaggregated results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy (discounted), PD-L1 ≥1% and any histology

Model outcome	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy
Progression-free survival time (in months)	19.61	20.71
Post-progression survival time (in months)	25.09	19.11
Life years	3.72	3.32
Discounted life years	**3.26**	**2.93**
Discounted QALYs; pre-progression	1.16	1.22
Discounted QALYs; progressive disease	1.22	0.93
Discounted QALYs lost due to adverse events	-0.002	-0.004
Discounted QALYs	**2.38**	**2.15**
Discounted drug acquisition and admin cost; pre-progression (£)	[redacted]	102,673
Discounted drug acquisition and admin cost; progressive disease (£)	[redacted]	715
Discounted disease management cost; pre-progression (£)	[redacted]	7,005

Model outcome	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy
Discounted disease management cost; progressive disease (£)	[redacted]	9,757
Discounted disease management cost; terminal care (£)	[redacted]	5,305
Discounted adverse event costs (£)	[redacted]	689
Discounted total cost (£)	[redacted]	**126,144**

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

B.3.7.2 Cost-comparison analysis (Alternative base case)

In the advisory board meeting conducted by Regeneron (see Section B.3.8.5), experts shared that they did not perceive any difference in efficacy data between EMPOWER-Lung 3 and KEYNOTE-189 or -407. A cost-comparison analysis, whereby efficacy and safety of pembrolizumab + chemotherapy was assumed equal to cemiplimab + chemotherapy, was conducted. The analysis was restricted to a two-year time horizon (as costs do not differ in the model past this point, so cancel out) and without discounting (in alignment with the NICE user guide for cost comparison (179)). The cost comparison scenario resulted in an incremental cost saving for cemiplimab + chemotherapy of [redacted] (see Table 66).

Table 66: Cost-comparison results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy (discounted), PD-L1 ≥1% and any histology

	Total cost (£)	Incremental cost (£)
Cemiplimab + chemotherapy	[redacted]	[redacted]
Pembrolizumab + chemotherapy	110,976	-

B.3.8 Exploring Uncertainty

B.3.8.1 Probabilistic sensitivity analysis

The probabilistic analysis (based on 1,000 iterations) resulted in cemiplimab + chemotherapy as a dominant treatment option versus pembrolizumab + chemotherapy (see Table 67). This was based on mean incremental costs of [redacted] and mean incremental QALYs of [redacted].

The cost-effectiveness plane and cost-effectiveness acceptability curves (CEAC) for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy are presented in Figure 30 and Figure 31, respectively.

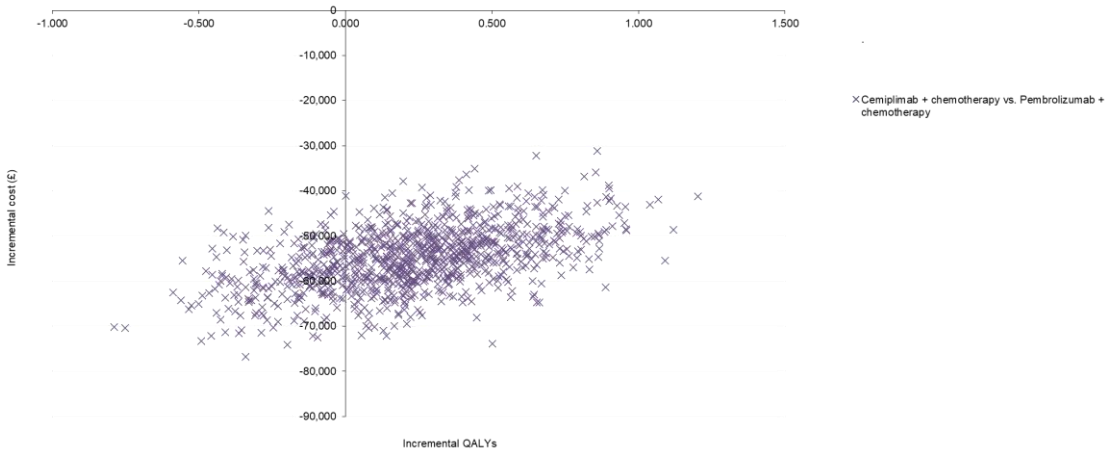
The cost-effectiveness plane shows probabilistic analysis iterations were spread primarily across the South-West quadrant, indicating cost savings and QALY losses for cemiplimab + chemotherapy (i.e., less costly and less effective) and the South-East quadrant, indicating cost savings and QALY gains for cemiplimab + chemotherapy (i.e., dominant). At a WTP threshold of £20,000-£30,000/QALY the probability of cost-effectiveness for cemiplimab + chemotherapy in the CEAC was 100% (Figure 31).

Table 67: Incremental results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy (discounted), probabilistic (1,000 iterations), PD-L1 ≥1% and any histology

	Total			Incremental			ICER (£)
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	
Cemiplimab + chemo	[redacted]	3.27	[redacted]	[redacted]	0.32	[redacted]	Dominant
Pembro + chemo	126,224	2.95	2.16	-	-	-	-

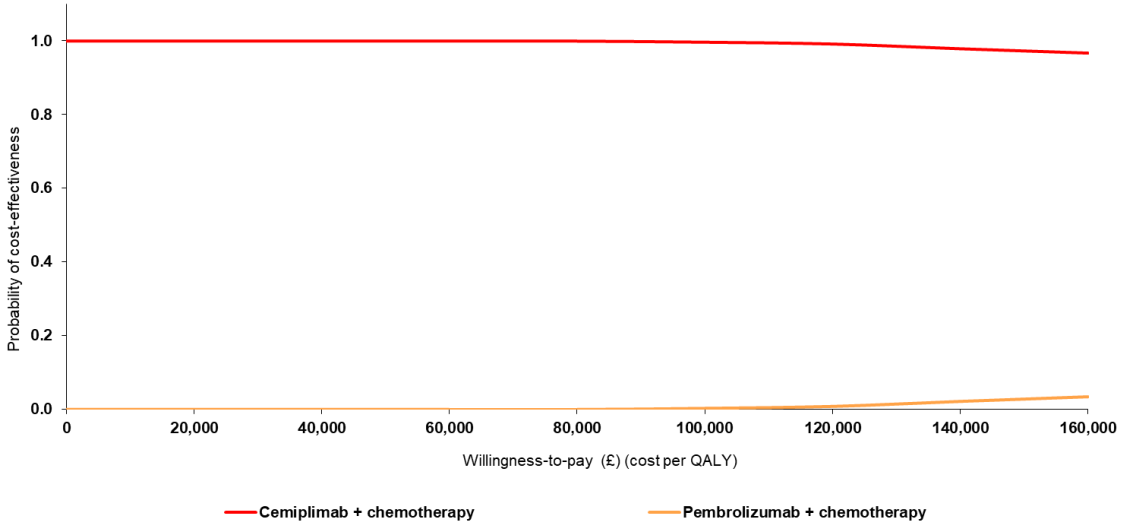
ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; pembro + chemo, pembrolizumab + chemotherapy

Figure 31: Probabilistic sensitivity analysis; scatter plot representing joint uncertainty distribution of cost-effectiveness of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy (1,000 iterations), PD-L1 ≥1% and any histology



QALYs, quality-adjusted life years.

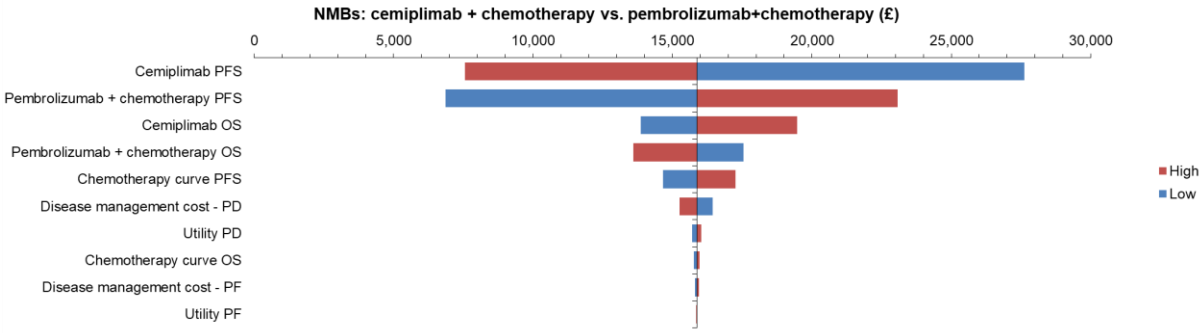
Figure 32: Cost-effectiveness acceptability curve for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy, PD-L1 ≥1% and any histology



B.3.8.2 One-way sensitivity analysis

Results of the OWSA are summarised as a tornado diagram in Figure 33 which includes the top most influential parameters for the comparison. Results of the analysis showed that the results were most sensitive to changes in the relative treatment effects from the NMA informing cemiplimab (+ chemotherapy) PFS and pembrolizumab (+ chemotherapy) PFS versus chemotherapy alone.

Figure 33: One one-way sensitivity analysis; tornado diagram of the NMB (£20,000 WTP threshold) of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy, PD-L1 ≥1% and any histology



NMB assuming a WTP threshold of £20,000.
NMB, net monetary benefit; OS, overall survival; PD, progressed disease, PF, progression-free; PFS, progression-free survival.

B.3.8.3 Deterministic scenario analyses

Alternative scenarios were evaluated to assess uncertainty regarding structural and methodological assumptions in the analysis (see Table 68).

Results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy were robust to changes in the PFS and OS distribution to potentially plausible alternatives. Scenario analysis explored the use of the log-normal for chemotherapy (reference) PFS and the two-step NMA, and generalised gamma distribution for chemotherapy (reference) OS and the two-step NMA. Cemiplimab + chemotherapy remained dominant across both alternative scenarios.

In a scenario estimating ToT through application of a PFS versus ToT HR the results remained dominant for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy, despite decreased total treatment costs for pembrolizumab + chemotherapy. Note that treatment beyond progression is not anticipated in clinical practice see Section B.3.5.1.

Recommendations from NICE TA683 and TA770 for pembrolizumab + chemotherapy recommend treatment up to 24 months; a similar 24-month treatment stopping rule was also applied for cemiplimab based on the EMPOWER-Lung 3 trial (38, 44). Scenario analyses explored waning of treatment effect assumptions following treatment stopping. Compared to the base case, where treatment effect waning was assumed after five years, waning of treatment effect applied to PFS/OS at three years and from three to five years resulted in dominant results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy for both scenarios. Results remained dominant for cemiplimab + chemotherapy for a scenario evaluating the use of alternative utility values and a scenario evaluating the use of Alternative subsequent treatment distributions informed by KEYNOTE-189 study, which aligned with the base case.

In a scenario analysis using the pooled KEYNOTE-189 and -407 studies to inform PFS and OS for the chemotherapy reference arm the results compared to pembrolizumab + chemotherapy remained dominant. Removing background mortality from the cost-comparison had a negligible impact on the cost savings

achieved by cemiplimab + chemotherapy. Similarly, removing AE costs and disutilities, and assuming no cost of drug wastage also had a negligible impact on the cost-utility results compared to the base case.

In threshold analyses, cemiplimab + chemotherapy was cost effective at the current cemiplimab NHS PAS price if the confidential discount to the NHS for pembrolizumab was at or below 60% and 63% at willingness-to-pay thresholds of £20,000/QALY and £30,000/QALY, respectively. In the cost-comparison analysis, cemiplimab was cost saving at the current NHS PAS price if the confidential discount for pembrolizumab was at or below 56%. If the confidential discount for pembrolizumab was assumed to be 65%, cemiplimab was no longer cost effective (in the cost-effectiveness analysis) nor cost saving (in the cost-comparison analysis).

Table 68: Results of scenario analyses, PD-L1 ≥1% and any histology

	Total			Incremental			ICER (£)
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	
Base case (PD-L1 ≥1% and any histology), two-step NMA (log-logistic PFS and OS)							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	126,144	2.93	2.15	-	-	-	-
Scenario 1: Alternative PFS reference and two-step NMA (log-normal)							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	126,471	2.93	2.15	-	-	-	-
Scenario 2: Alternative OS reference and two-step NMA (generalised gamma)							
Cemiplimab + chemo	[redacted]	2.69	[redacted]	[redacted]	0.28	[redacted]	Dominant
Pembro + chemo	122,579	2.41	1.79	-	-	-	-
Scenario 3: PFS constant HR NMA (log-logistic), no violation of PH assumption for PFS							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	118,433	2.93	2.15	-	-	-	-
Scenario 4: Applying HRs to PFS to estimate time on treatment							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	116,751	2.93	2.15	-	-	-	-
Scenario 5: Waning of treatment effect applied to PFS/OS from 36 months							
Cemiplimab + chemo	[redacted]	3.06	[redacted]	[redacted]	0.24	[redacted]	Dominant
Pembro + chemo	125,600	2.82	2.07	-	-	-	-

	Total			Incremental			ICER (£)
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	
Scenario 6: Waning of treatment effect applied to PFS/OS from 36 to 60 months							
Cemiplimab + chemo	[redacted]	3.19	[redacted]	[redacted]	0.30	[redacted]	Dominant
Pembro + chemo	125,971	2.89	2.12	-	-	-	-
Scenario 7: Continuation of treatment effect (no waning applied)							
Cemiplimab + chemo	[redacted]	3.42	[redacted]	[redacted]	0.42	[redacted]	Dominant
Pembro + chemo	126,428	3.00	2.20	-	-	-	-
Scenario 8: Alternative health state utility values (NICE TA584 atezo+bev+chemo non-squamous IMpower 150 utilities using UK tariff)							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	126,144	2.93	2.02	-	-	-	-
Scenario 9: Alternative subsequent treatment distribution							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	137,939	2.93	2.15	-	-	-	-
Scenario 10: Hypothetical discount applied to pembrolizumab list price: 65% in the cost-utility analysis							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	[redacted]
Pembro + chemo	61,879	2.93	2.15	-	-	-	-
Scenario 11: Hypothetical discount applied to pembrolizumab list price: 65% in the cost-comparison analysis							
Cemiplimab + chemo	[redacted]	1.50	[redacted]	[redacted]	0.00	0.00	Equal QALY
Pembro + chemo	48,942	1.50	1.13	-	-	-	-
Scenario 12: Alternative reference arm based on pooled KEYNOTE studies (log-logistic for PFS and OS)							
Cemiplimab + chemo	[redacted]	3.64	[redacted]	-	-	-	-
Pembro + chemo	126,178	3.31	2.42	[redacted]	0.33	[redacted]	Dominant
Scenario 13: Exclude AE costs and disutilities							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	125,455	2.93	2.15	-	-	-	-
Scenario 14: Assume no drug wastage							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	126,115	2.93	2.15	-	-	-	-
Scenario 15: Cemiplimab + chemotherapy patients receive AUC5 carboplatin instead of AUC6							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	126,144	2.93	2.15	-	-	-	-
Scenario 16: 75% of pembrolizumab + chemotherapy patients switch to pembrolizumab monotherapy Q6W after 4-months of treatment							

	Total			Incremental			ICER (£)
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	126,362	2.93	2.15	-	-	-	-
Scenario 17: Include AE costs from KEYNOTE 189 and KEYNOTE 407 in the pembrolizumab + chemotherapy arm of the cost-comparison analysis (instead of assuming equal to EMPOWER-Lung 3)							
Cemiplimab + chemo	[redacted]	1.50	[redacted]	[redacted]	0.00	0.00	Equal QALY
Pembro + chemo	111,317	1.50	1.13	-	-	-	-

HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life year; NMA, network meta-analysis; OS, overall survival; PFS. Progression-free survival; QALY, quality-adjusted life year; pembro + chemo, pembrolizumab + chemotherapy.

B.3.8.4 Subgroup Analyses

Alternative scenarios evaluating subgroups of interest to NICE based on histology and PD-L1 levels were evaluated as part of the analysis:

- Squamous, PD-L1 1-49%
- Squamous, PD-L1 ≥50%
- Non-squamous, PD-L1 1-49%
- Non-squamous, PD-L1 ≥50%

The results of the scenario analysis evaluating these subgroups are reported in Table 69. Model selection for each subgroup was based only on the optimal/most favoured NMA model. The methods used for the extrapolation of treatment effect for each of the subgroups included in the analysis are detailed in Appendix Q.

Compared to the base case, the PD-L1 1-49% squamous and PD-L1 1-49% non-squamous results remained dominant. As there were no violations in the PH assumption for PFS and OS across the PD-L1 1-49% squamous and non-squamous subgroups. Additional scenarios were run using the constant HR NMAs, in which results remained dominant for the PD-L1 groups. The PD-L1 ≥50%, squamous histology subgroup resulted in an ICER indicating that cemiplimab + chemotherapy was less costly and less effective than pembrolizumab + chemotherapy. An analysis using the constant HR NMA to facilitate a comparison to pembrolizumab (KM curves not available for pembrolizumab monotherapy) suggested that cemiplimab + chemotherapy was less costly and less effective than pembrolizumab in the PD-L1 ≥50%, squamous histology subgroup. The PD-L1 ≥50%, non-squamous histology subgroup indicated that cemiplimab + chemotherapy was dominant to

pembrolizumab + chemotherapy, in alignment with the base case. An analysis using the constant HR NMA to facilitate a comparison to pembrolizumab (KM curves not available for pembrolizumab monotherapy) also resulted in a dominant ICER in the PD-L1 ≥50%, non-squamous histology subgroup, in line with the base case.

Although the model incorporates robust statistical methods to inform relative treatment effects (i.e., two-step multivariate NMA) and also only includes comparisons between outcomes from similar populations to reduce heterogeneity (i.e., by PD-L1 expression and histology), caution should be taken in drawing conclusions about relative efficacy of cemiplimab + chemotherapy versus comparators particularly where sample sizes in subgroups of subgroups are small.

Table 69: Results of subgroup analyses

	Total			Incremental			ICER (£)
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	
Base case results (PD-L1 ≥1%, any histology)							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	126,144	2.93	2.15	-	-	-	-
Scenario 18: PD-L1 1-49% squamous histology subgroup, assuming two-step NMA (exponential for OS and log-logistic for PFS) [a]							
Cemiplimab + chemo	[redacted]	2.34	[redacted]	[redacted]	0.30	[redacted]	Dominant
Pembro + chemo	100,943	2.04	1.52	-	-	-	-
Scenario 19: PD-L1 1-49% squamous histology subgroup, assuming constant HR NMA (exponential for OS and log-logistic for PFS)[a]							
Cemiplimab + chemo	[redacted]	2.33	[redacted]	[redacted]	0.27	[redacted]	Dominant
Pembro + chemo	100,948	2.06	1.53	-	-	-	-
Scenario 20: PD-L1 ≥50%, squamous histology subgroup, assuming two-step NMA (gamma for OS and log-logistic for PFS) [a]							
Cemiplimab + chemo	[redacted]	2.19	[redacted]	[redacted]	-0.44	[redacted]	Less costs and less effective
Pembro + chemo	141,339	2.63	1.95	-	-	-	-
Scenario 21: PD-L1 ≥50%, squamous histology subgroup, assuming constant HR NMA (gamma for OS and log-logistic for PFS)[b]							
Cemiplimab + chemo	[redacted]	2.18	[redacted]	[redacted]	-0.19	[redacted]	Less costs and less effective
Pembro + chemo	116,319	2.37	1.76	-	-	-	-
Scenario 22: PD-L1 1-49% non-squamous histology subgroup, assuming two-step NMA (log-logistic for OS and log-logistic for PFS) [a]							

	Total			Incremental			ICER (£)
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	
Cemiplimab + chemo	[redacted]	3.31	[redacted]	[redacted]	0.37	[redacted]	Dominant
Pembro + chemo	118,961	2.93	2.14	-	-	-	-
Scenario 23: PD-L1 1-49% non-squamous histology subgroup, assuming constant HR NMA (log-logistic for OS and log-logistic for PFS)[a]							
Cemiplimab + chemo	[redacted]	3.76	[redacted]	[redacted]	0.87	[redacted]	Dominant
Pembro + chemo	113,968	2.89	2.11	-	-	-	-
Scenario 24: PD-L1 ≥50%, non-squamous histology subgroup, assuming two-step NMA (log-logistic for OS and log-logistic for PFS) [a]							
Cemiplimab + chemo	[redacted]	3.45	[redacted]	[redacted]	0.63	[redacted]	Dominant
Pembro + chemo	143,608	2.82	2.10	-	-	-	-
Scenario 25: PD-L1 ≥50%, non-squamous histology subgroup, assuming constant HR NMA (log-logistic for OS and log-logistic for PFS)[a,c]							
Cemiplimab + chemo	[redacted]	3.40	[redacted]	[redacted]	1.14	[redacted]	Dominant
Pembro + chemo	130,765	2.26	1.70	-	-	-	-

[a]No violation of PH assumption for either PFS or OS in any trials in this subgroup; [b]Violation in the PH assumption for OS in KEYNOTE-407; [c]Violation in the PH assumption for OS in KEYNOTE-189.
HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life year; NMA, network meta-analysis; OS, overall survival; PFS. Progression-free survival; QALY, quality-adjusted life year; pembro + chemo, pembrolizumab + chemotherapy.

B.3.8.5 Validation

The first version of the model parameterised with source data underwent validation in accordance with NICE methods guidance (180):

Technical verification and evaluation of internal consistency to ensure there were no structural, calculation or programming errors

- Technical verification was conducted consistent with the TECH-ver checklist (see Appendix P).
- Technical verification was carried out by a senior member of the project team (modelled) not involved in the programming and checked formulas, calculations, links between cells (Microsoft Excel) and syntax (Visual Basic).
- Extreme value analysis was performed to determine whether the model output was consistent with input variation to help identify any remaining errors.

Internal consistency was also evaluated by comparing the model outputs with source data used for the model development.

- For example, modelled PFS, OS and ToT were overlayed with the KM data informing the extrapolations to ensure the appropriateness of extrapolations.

Cross validation was performed by comparing the results of the developed model (particularly for PFS and OS) for the interventions of interest with clinical outcomes.

- Predicted OS estimates were compared versus country-specific general population mortality during the model selection process to consider when OS curves intersected with general population mortality.

- Extrapolations of PFS and OS were cross validated against relevant clinical data from comparator trials.

Regeneron conducted an advisory board meeting (24 May 2024), which was attended by 10 medical and clinical oncologists who routinely treat patients with locally advanced or metastatic NSCLC and are based at a representative set of centres (both urban and rural) in England. The meeting validated key model assumptions, including validation of base case model selection for extrapolation of PFS and OS, and validation of ToT assumptions. Follow-up questions have been shared with experts to validate adverse event rates, health state utility values, assumptions around drug administration (i.e., distribution of chemotherapies, receipt of pemetrexed maintenance, subsequent treatment assumptions and health care resource use in the PF and PD health states.

Based on the findings, the model was corrected and updated where necessary. The results of the validation are reported in Appendix P.

B.3.9 Discussion

The aim of this analysis was to evaluate the cost-effectiveness of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy for the treatment of adult patients with previously untreated locally advanced (not a candidate for definitive chemoradiation) or metastatic NSCLC which expresses PD-L1 on 1% or more of

tumour cells and has no EGFR, ALK or ROS-1 genetic alterations. The PD-L1 ≥1%, any histology population included in the economic evaluation base case was consistent with the untreated advanced or metastatic NSCLC population eligible for cemiplimab + chemotherapy as per its UK marketing authorisation. The economic evaluation reflects patients assessed in the Phase 3 EMPOWER-Lung 3 clinical trial and is relevant to all subgroups of patients (PD-L1 1-49 vs ≥1%, squamous vs non-squamous) in whom pembrolizumab + chemotherapy is the current SOC IO + chemotherapy option, and who could potentially benefit from availability of an alternative IO + chemotherapy option with a protocol that provides greater flexibility to tailor chemotherapy treatment to individual patient needs and preferences. A cost-effectiveness analysis was developed to model costs and health outcomes over a 30-year lifetime horizon. The perspective of the analysis was NHS and PSS health care payer perspective, the first economic evaluation of this treatment combination and indication from a UK healthcare payer perspective.

The methods used in this analysis are based on best practice guidelines and a modelling approach that is consistent with established methods for advanced patients in oncology (110, 181). A partitioned survival model structure with a monthly cycle length was used in the analysis. The advantage of this model structure is that it leverages OS and PFS data directly to model patient outcomes, which are usually the primary and secondary endpoints in the pivotal clinical trials. To extrapolate OS and PFS over a lifetime horizon, parametric distributions were fit to the KM curves for the chemotherapy arm of the EMPOWER-Lung 3 trial. In the base case, time-varying hazard ratios derived from an NMA including EMPOWER-Lung 3, KEYNOTE-189 and KEYNOTE 407 were applied to the extrapolated EMPOWER-Lung 3 chemotherapy PFS and OS to derive outcomes for the other treatments included in the network. The area underneath the OS and PFS curves were used to determine the percentage of patients in the PF, PD, and death health states over time. Utility values for the PF and PD health states were derived from EORTC QLQ-C30 data collected in EMPOWER Lung-3 mapped to the EQ-5D-3L, using Longworth et al (2014)(126) mapping algorithm and the Dolan et al (1997) UK tariff (131). The analysis included costs related to drug acquisition, administration, disease management, terminal care, and treatment of adverse events.

For the base case analysis in the PD-L1 ≥1%, any histology (ie, MHRA label) population and using the UK PAS price for cemiplimab of [redacted] per 350 mg vial, the incremental cost per QALY gained was dominant (i.e. lower total costs and higher total QALYs) versus pembrolizumab + chemotherapy. These results were based on incremental costs of [redacted] versus pembrolizumab + chemotherapy (incremental pre-progression drug acquisition and administration cost of [redacted]). The incremental QALYs were [redacted] versus pembrolizumab + chemotherapy ([redacted] in the PF state, [redacted] in the PD state). At a £20,000 WTP threshold the probability that cemiplimab + chemotherapy is the more cost-effective treatment is 100% in the CEAC. These results are based on the PAS and list prices for cemiplimab and pembrolizumab, respectively, whereas price discounts are already implemented for both therapies in agreements with NHS England.

Scenario analyses were conducted to evaluate uncertainty regarding structural and methodological assumptions in the analysis. Uncertainty in the predicted long-term OS estimates was a key limitation of the cost-effectiveness analysis. Follow-up from EMPOWER-Lung 3 trial was incomplete; at 30 months, 33.1% of patients receiving cemiplimab + chemotherapy and 16.4% patients receiving chemotherapy remained at risk (i.e., alive). Although methods recommended in NICE DSU 14 and 21 were used to guide the extrapolation of PFS and OS over the lifetime horizon of the model, there remains uncertainty in the true long-term survival benefit of cemiplimab + chemotherapy and pembrolizumab + chemotherapy (181, 182). The chemotherapy arm of the EMPOWER-Lung 3 trial was selected as the reference data source in the model, as it was the control arm for the EMPOWER-Lung 3 trial for which IPD is available. An advantage to anchoring the relative treatment effects to the chemotherapy arm from EMPOWER-Lung 3 is that the estimated PFS and OS for cemiplimab + chemotherapy can be validated against the cemiplimab + chemotherapy KMs from the EMPOWER-Lung 3 trial allowing for assessment of internal validity of the relative treatment effects from the NMA. Although longer follow-up is available from the KEYNOTE 407 and 189 studies, using the EMPOWER-Lung 3 as a reference better aligns with the target population for this analysis (i.e., the EMPOWER-Lung 3 population). External estimates of chemotherapy survival suggested 5-11% of patients are alive at five years (40, 44,

96), however only three models predicted survival estimates within that range (log-normal, log-logistic, and generalised gamma [fixed Q]). The log-logistic, which predicts in the middle of the three distributions, was selected as the base case and validated by UK clinical experts (see Section B.3.8.5). Scenario analysis using the generalised gamma and log-normal both resulted in a dominant result versus pembrolizumab + chemotherapy.

In the advisory board meeting (see Section B.3.8.5), experts shared that they did not perceive any meaningful differences in efficacy data between EMPOWER-Lung 3 and KEYNOTE-189 or -407 studies, and suggested that efficacy outcomes for cemiplimab + chemotherapy would be expected to be broadly consistent with those seen with pembrolizumab + chemotherapy in UK clinical practice. The experts also noted the low rates of some AEs (e.g., immune-mediated AEs) in EMPOWER-Lung 3, but were cautious about drawing conclusions in the absence of robust head-to-head evidence, with differences potentially owing to IO experience bias or reporting differences between trials.

There is uncertainty related to the duration of treatment benefit of IOs following treatment cessation at 24 months. The base case includes a five-year waning assumption, whereby at five-years the PFS and OS hazards for cemiplimab + chemotherapy and pembrolizumab + chemotherapy are assumed equal to chemotherapy. A five-year waning time-point was supported by five-year follow-up from KEYNOTE-189 and 407 demonstrating a continued benefit beyond treatment stopping. It was also supported by UK clinical experts (see Section B.3.8.5) who provided feedback that it is reasonable to generalise LTFU data for pembrolizumab and assume the same waning duration for cemiplimab in the cost-utility model, and has been used in 50% of NICE appraisals applying waning assumptions (183). Scenario analyses evaluated the sensitivity of the results to this assumption. Application of waning at 36 months resulted in a dominant ICER versus pembrolizumab + chemotherapy. Assumption of a continued treatment benefit (i.e., no waning applied) resulted in a dominant versus pembrolizumab + chemotherapy.

The EMPOWER-Lung 3 protocol allowed patients to continue treatment beyond initial RECIST 1.1-defined progressive disease if the investigator perceived the

patient to be experiencing clinical benefit and if the patient had not completed the 108-week treatment period. However, the MHRA label for cemiplimab specifies that cemiplimab treatment “may be continued until disease progression or unacceptable toxicity”. Based on the MHRA label, it is not anticipated that treatment will continue beyond progression in clinical practice as it did in the clinical trial for some patients. Although the base case assumed ToT was equal to PFS, a scenario estimating ToT through application of a PFS versus ToT HR still resulted in dominant ICER for cemiplimab + chemotherapy.

Alternative scenarios evaluated subgroups of interest to NICE, specifically the PD-L1 1-49% squamous and non-squamous, and the PD-L1 ≥50% squamous and non-squamous. Model selection for each subgroup was based only on the optimal/most favoured NMA model and did not consider goodness of fit to the reference arm (i.e., chemotherapy), long-term survival estimates or clinical validation. Compared to the base case, results across the four NICE subgroups analysed remained dominant or cost-effective, (see Section B.3.8.5). The consistency of results across subgroups supports Regeneron’s view that the PD-L1 ≥ 1% any histology population should be the key and only population considered for decision making.

The analysis based the distribution of chemotherapies across IO combinations on reported data from EMPOWER-Lung 3. There were differences in platinum doublet chemotherapies investigated in EMPOWER-Lung 3 (pemetrexed or paclitaxel in combination with platinum chemotherapy) compared to platinum doublet chemotherapies investigated in comparator studies (i.e., KEYNOTE-407 evaluated pembrolizumab in combination with either paclitaxel or nab-paclitaxel and carboplatin). The chemotherapy distributions and doses were aligned in the model as differences are not anticipated in the real-world use of chemotherapy in combination with cemiplimab or pembrolizumab. Although the EMA license for pembrolizumab in non-squamous NSCLC allows for use in combination with nab-paclitaxel and carboplatin, evaluation of UK market data from Regeneron confirmed that nab-paclitaxel is rarely used therefore removal of nab-paclitaxel from the decision problem was reflective of clinical practice in the UK (2). Likewise, the EMA license for pembrolizumab in squamous and non-squamous patients allows for the use of cisplatin with either pemetrexed or paclitaxel. Although UK clinical expert lung

oncologist feedback confirmed that cisplatin is rarely used in clinical practice in the UK, it was retained in the model given that the proportions in EMPOWER-Lung 3 were small, costs and efficacy would not differ substantially from those of carboplatin and costs would largely cancel out between model arms given that the same distribution of chemotherapies was assumed.

As EQ-5D was not collected in EMPOWER-Lung 3, HSUVs in the base case analysis were derived through mapping EORTC QLQ-C30 data collected from EMPOWER-Lung 3 to the EQ-5D-3L preference-based measure. The use of a mapping model inevitably introduces uncertainty into HSUV estimates because of prediction error. Uncertainties in the outcomes of this analysis were further exacerbated by the incomplete follow-up at the time of the analysis (median follow-up 28.4 months) and the limited number of completed questionnaires amongst patients with progressed disease at the time of assessment. Despite these uncertainties, changes in the HSUVs had a relatively small impact on the results as demonstrated by the OWSA and scenario analyses. Mapping algorithms were identified based on an extensive search of literature and HTA submissions, which identified 27 unique algorithms. Published comparisons of the identified algorithms showed that the Longworth 2014 (126) algorithm used in the analysis had been validated in multiple settings and had been endorsed by multiple authors (127, 129). A systematic literature review (Section B.3.4.4) found HSUVs reported in the literature to generally be lower than those included in the current analysis. Further, HSUVs from the literature generally reported greater differences between the progression-free and progressed HSUVs compared to those included in the current study. Reviews validating mapping algorithms noted that algorithms tended to overpredict HSUVs more frequently at poorer health states, while good health tended to be estimated well (127, 129). As such, HSUVs estimated in the mapping analysis for progressed disease may have been overestimated, contributing to the comparatively higher post-progression estimates and leading to a smaller incremental difference compared to the literature. In a scenario evaluating alternative utility values results remained dominant for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy.

While Regeneron acknowledges that cemiplimab in combination with chemotherapy was routed via the single technology appraisal process, which dictates that a cost-utility analysis should be conducted, we have also presented a cost comparison analysis. The rationale for this is explained in detail at the beginning of Section B.3, but in summary relates to the conclusion from the NMA that there were no statistically significant differences in efficacy between cemiplimab + chemotherapy and pembrolizumab + chemotherapy. This assumption of equal efficacy between IOs was further confirmed by UK clinical expert lung oncologists as being a justified approach. While results in this submission show that cemiplimab + chemotherapy is cost-saving vs. pembrolizumab + chemotherapy at the pembrolizumab list price, subject to commercial discussions with NHS England, Regeneron aims to provide cemiplimab + chemotherapy at a price to the NHS that is net cost saving in the context of the current confidential PAS price in place for pembrolizumab.

B.3.10 Conclusion

In the absence of head-to-head data versus the relevant comparator for this appraisal (i.e., pembrolizumab + chemotherapy) and given limitations associated with cost-utility analysis approach to address the decision problem as outlined at the start of Section B.3, Regeneron believes that currently, the justification for modelling equivalent efficacy for cemiplimab + chemotherapy and pembrolizumab + chemotherapy is stronger than the justification for modelling any differences in efficacy.

A cost comparison analysis assuming equivalent clinical outcomes for cemiplimab + chemotherapy and pembrolizumab + chemotherapy in the PD-L1 ≥1%, any histology (MHRA label) population was therefore included as an 'alternative base case'. Subject to commercial discussions with NHS England, Regeneron aims to provide cemiplimab + chemotherapy at a price to the NHS that is net cost saving in the context of the current confidential PAS price in place for pembrolizumab. This cost comparison analysis is potentially conservative as it does not account for any potential clinical or cost benefits that could result from giving clinicians greater upfront flexibility to tailor chemotherapy dose/agent to individual patient characteristics, needs, and preferences beyond the limited current SoC options.

Given the anticipated similar efficacy outcomes in UK clinical practice, combined with greater flexibility in the choice of background chemotherapy, cemiplimab + chemotherapy should be recommended as a highly clinically effective and cost-effective alternative treatment option for patients meeting its licensed indication which represents a low risk to the NHS.

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Appendices

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Summary of Information for Patients (SIP)

September 2024

File name	Version	Contains confidential information	Date
	2.0	**No**	**25SEP2024**

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Cemiplimab (Libtayo®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults with non-small-cell lung cancer (NSCLC) who have a protein called programmed cell death ligand-1 (PD-L1) on at least 1% of their cancer cells and no mutations in the *EGFR*, *ALK* or *ROS1* genes. Patients must have either disease that has spread to nearby tissue or lymph nodes (locally advanced disease) that cannot be treated with chemotherapy and radiation or disease that has spread to other areas of the body (metastatic disease).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Cemiplimab in combination with platinum-based chemotherapy was approved for use in NSCLC by the European Medicines Agency (the organisation that gives companies the legal right to sell medicines in the European Union) in March 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/libtayo In the UK, the Medicines and Healthcare products Regulatory Authority (MHRA) gave its approval (EU Reliance Route) in February 2024. The marketing authorisation number is: PLGB 45232/0001

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Regeneron provides an annual contribution of £30,000 to the Global Lung Cancer Coalition (GLCC) which is a loose coalition of registered charitable/not-for-profit organisations. Since the beginning of 2005, the GLCC has been administered by the Roy Castle Lung Cancer Foundation (RCLCF), a UK based charity and GLCC member. All corporate governance and financial structures of the GLCC are through the RCLCF and carried out under UK charity law. Regeneron's contribution to GLCC through the RCLCF is to broadly support the coalition's overall mission and annual workplans that carry our GLCC's commitment to "improving disease outcomes for all lung cancer patients."

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Lung cancer is the third most common cancer and the leading cause of cancer-related deaths in the UK (1). There are two main types of lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC is the most common, accounting for approximately 85% to 90% of cases (2).

NSCLC can be further divided into subtypes:

- Squamous cell cancer - starts in squamous cells (the flat cells lining the inside of the airways in the lung) and represents approximately 25% to 30% of NSCLC cases in the UK (2)
- Non-squamous cell cancer – includes adenocarcinoma and large cell cancer. Adenocarcinoma starts in epithelial cells, which are the cells in the lung that make mucus. Large cell cancer can start in any part of the lung. Non-squamous cell cancer makes up approximately 70% to 75% of NSCLC cases in the UK (2)

People with early-stage NSCLC often don't have any symptoms, so most are not diagnosed until they have advanced disease. People with advanced disease often have a cough and may cough up blood. Other symptoms include loss of appetite, unexplained weight loss and tiredness.

It is estimated that there will be approximately 4,844 people diagnosed with advanced or metastatic NSCLC in England who will receive systemic anticancer therapy and would be eligible for treatment with cemiplimab + chemotherapy within its licensed indication in 2025, rising to 5,143 in 2029.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
Lung cancer is diagnosed using a combination of chest X-rays, scans, bronchoscopy (a procedure that allows) and biopsy (taking a small sample of cells). Patients are also tested for genetic mutations and PD-L1 levels, both of which help doctors to decide on the best treatment option. At diagnosis, the cancer will be staged by assessing the size and characteristics of the tumour, whether the cancer has spread to local lymph nodes (small bean-shaped structures that contain white blood cells, which fight infection) and whether it has spread to distant tissues or organs. The stages range from 0 (early disease) to IV (metastatic disease). No additional diagnostic tests are required with cemiplimab plus chemotherapy.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed: • What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP. • Please also consider: o if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data. o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
For people with NSCLC who do not have genetic mutations that can be treated with a targeted treatment, immunotherapy (with or without chemotherapy) is the usual first treatment (unless there is a reason why they cannot take it). Available treatment options vary according to the patient's PD-L1 levels and whether they have squamous or non-squamous disease (see the current NICE NSCLC guideline for further information: https://www.nice.org.uk/guidance/ng122). Immunotherapy + chemotherapy is the only routinely available immuno-oncology drug (IO)-based option for people with PD-L1 levels 1-49% and is therefore standard of care in this population. For people with PD-L1 ≥ 50%, both IO monotherapy and IO + chemotherapy are routinely available as treatment options, and clinicians face more complex decision making regarding which might be the most suitable option given heterogeneous patient characteristics, needs, and preferences. Pembrolizumab is by far the most frequently used IO in people with locally advanced or metastatic NSCLC for whom IO + chemotherapy is considered the most appropriate choice, with >80% of the current market share among people with squamous/non-squamous disease and PD-L1 levels ≥1%

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

During the health technology appraisal process for cemiplimab plus chemotherapy in Canada, feedback was gathered from the Lung Health Foundation/The Ontario Lung Association (3). The information provided from the Lung Health Foundation was obtained from an online survey completed by 15 patients living with lung cancer and one caregiver. Information on age, gender and geographical location was not collected from any of the 15 online respondents. All of the online respondents completed the survey between January 2021 and October 2023.

Side-effects were highlighted as a particular source of distress. Some patients said they had no symptoms from the cancer but struggled with side-effects from their treatment. Patients said that maintaining quality of life is important and that they would like treatments with minimal side effects so they can carry on with regular activities while on treatment.

Caregivers also said they find it challenging to watch patients suffer with side-effects and that they feel conflicted between wanting the patient to get treatment but not wanting them to have side-effects (3).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Cemiplimab is a type of immunotherapy. It stimulates the immune system to attack cancer cells by targeting and blocking a protein called programmed cell death protein 1 (PD-1) on the surface of a type of immune cell called T cells. Blocking PD-1 triggers the T cells to find and kill cancer cells.

As described in Section 3h, there is the potential for cemiplimab to be combined with a wider range of chemotherapy doses/treatments than is routinely possible with the current standard of care immunotherapy (pembrolizumab). Side effects from chemotherapy represent a high burden to people living with advanced/metastatic NSCLC; in some cases, the treatment burden is higher than the symptom burden of the cancer. Feedback from a geographically representative group of clinical expert lung oncologists who routinely treat NHS patients in England was solicited by Regeneron at an advisory board and follow-up discussions held during May to August 2024. The clinical experts explained that the option to initiate treatment with carboplatin at a lower dose for people with squamous disease (AUC5), and to use an alternative to pemetrexed for people with

non-squamous disease (e.g. paclitaxel), alongside an IO would be “helpful” and “useful”. This flexibility may benefit, for example, older people, those with renal, cardiac, or hepatic impairment, or those with a high comorbidity burden.

The summary of product characteristics for cemiplimab is available here: https://www.medicines.org.uk/emc/product/10438.

The patient information leaflet is available here https://www.medicines.org.uk/emc/product/10438/pil#about-medicine

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

This appraisal relates to cemiplimab (an immunotherapy) given in combination with platinum-based chemotherapy.

Immunotherapy (e.g. pembrolizumab) in combination with platinum-based chemotherapy is a standard of care treatment option and the side effects of chemotherapy (including in combination with immunotherapy) are well documented.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Cemiplimab 350 mg can be given by infusion into a vein once every 3 weeks until disease progression or unacceptable toxicity; and chemotherapy is given once every 3 weeks for 4 cycles.

As is the case with other IO + chemotherapy options, Regeneron anticipates that use of cemiplimab in the NHS would be for up to a maximum duration of 2 years as per the design of the EMPOWER-Lung 3 study discussed below.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

One clinical trial has assessed cemiplimab plus chemotherapy for the treatment of NSCLC: EMPOWER-Lung 3 (NCT03409614). The study was carried out in China, Georgia, Greece, Malysia, Poland, Romania, Russia, Thailand, Turkey and Ukraine. It enrolled adults with locally advanced or metastatic squamous or non-squamous NSCLC and any level of PD-L1 on their cancer cells. To take part, participants had to have a life expectancy of at least 3 months. They were not allowed to

take part if their cancer had spread to the brain and was not treated or unstable, if the tumour was pressing on the spinal cord, or if they had mutations in the *EGFR*, *ALK* or *ROS1* genes.

The study measured the effect of cemiplimab + chemotherapy on:

- overall survival (the length of time from the start of treatment to death from any cause);
- progression free survival (the length of time from the start of treatment until disease progression or death from any cause);
- treatment response rates (the proportion of participants who had either a complete or partial response to treatment).

Participants were randomly allocated to cemiplimab plus chemotherapy or placebo plus chemotherapy. The allocation of treatments was double-blinded, which means neither the participants nor the people running the study knew which treatment each patient was taking. Treatment lasted for up to 108 weeks, unless that patient's cancer got worse or they had unacceptable side-effects.

In total, 466 participants were enrolled: 312 received cemiplimab + chemotherapy and 154 received placebo plus chemotherapy.

The trial was stopped early as it met the criteria for demonstrating an overall survival benefit. There are several publications that describe the results of the study (4-7).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

EMPOWER-Lung 3 included participants with PD-L1 on any percentage of their cancer cells, whereas in the UK, cemiplimab plus chemotherapy is approved for use in people who have PD-L1 on 1% or more of their cancer cells. Because of this, the results included in the company's submission to NICE focus on a subset of participants from EMPOWER-Lung 3 who had PD-L1 on 1% or more of their cancer cells (referred to as the 'MHRA label population').

The MHRA label population included 327 participants (217 who received cemiplimab plus chemotherapy and 110 who received placebo + chemotherapy). Results from this population have recently been published (7).

In the MHRA label population:

- participants who received cemiplimab + chemotherapy had longer overall survival than those who received placebo plus chemotherapy (23.5 months vs 12.1 months).
- participants who received cemiplimab + chemotherapy had longer progression-free survival than those who received placebo plus chemotherapy (8.3 months vs 5.5 months).
- more than twice as many participants who received cemiplimab plus chemotherapy had either a complete or partial response to treatment, compared with placebo plus chemotherapy (47.9% vs 22.7%).
- response to treatment was notably longer with cemiplimab plus chemotherapy than with placebo plus chemotherapy (17.5 months vs 6.5 months).

Although there are no trials that directly compare cemiplimab plus chemotherapy with pembrolizumab plus chemotherapy, it is possible to compare them indirectly. The company carried out an indirect comparison; the results are not published but showed comparability in efficacy and safety between cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy. However, it is important to note that the analysis included meaningful limitations. Overall, the collective evidence from clinical trials, the indirect treatment comparison, and clinical expert feedback provided to the company strongly suggests there are no clinically meaningful differences in outcomes between cemiplimab + chemotherapy and pembrolizumab + chemotherapy.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In EMPOWER-Lung 3, participants' quality of life was measured using the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires (6).

The EORTC QLQ-C30 is designed to measure physical, psychological and social function in all cancer patients. The EORTC QLQ-LC13 was developed specifically for use in people with lung cancer.

People treated with cemiplimab plus chemotherapy reported a marked improvement in pain symptoms compared with those treated with placebo plus chemotherapy (6). They also had markedly longer times to meaningful worsening of physical functioning, role functioning, nausea/vomiting, pain, alopecia (hair loss), dyspnoea (shortness of breath), cough and sore mouth then those who received placebo plus chemotherapy (6). All other measures were similar between the two treatment groups.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had

treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In EMPOWER-Lung 3, the percentage of participants who had side effects was similar between treatment groups: 96.5% with cemiplimab + chemotherapy and 94.8% with placebo + chemotherapy (8). The most common side-effects with both treatments were anaemia (too few healthy red blood cells), alopecia (hair loss) and nausea (Table 1). Very few participants withdrew from the study because of side effects with cemiplimab plus chemotherapy (6.1% compared with 2.6% who received placebo plus chemotherapy).

Table 1 Most common side effects in the EMPOWER-Lung 3 trial

	Number (%) of participants	
	Cemiplimab + chemo (n = 312)	**Placebo + chemo (n = 153)**
Headache	143 (45.6)	61 (39.9)
Nasopharyngitis	116 (37.2)	67 (43.8)
Hot flushes	79 (25.3)	25 (16.3)

The side-effects reported with cemiplimab plus chemotherapy are typical of those seen with other immunotherapies. No additional safety concerns were identified for cemiplimab plus chemotherapy.

Immunotherapies are associated with a number of specific immune-related side effects, including pneumonitis (inflammation of the lungs), nephritis (inflammation of the kidneys), colitis (inflammation of the large intestine) and rash. In EMPOWER-Lung 3, 18.9% of participants had immune-related side-effects (5); for several of these, the rates were lower than previously seen in clinical trials of pembrolizumab plus chemotherapy (9, 10)

See the patient information leaflet for further details.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

In people with squamous disease who are more suitable for immunotherapy in combination with chemotherapy, current practice is to give an immunotherapy called pembrolizumab in combination with a high dose (AUC6) of a chemotherapy called carboplatin; people with non-squamous disease are given pembrolizumab in combination with pemetrexed. Both of these chemotherapies are associated with significant toxicities and may not be suitable for all patients.

In EMPOWER-Lung 3, cemiplimab could be initiated with a lower dose of carboplatin (AUC5) for people with squamous disease and could be combined with non-pemetrexed chemotherapy (paclitaxel + carboplatin) for people with non-squamous disease (4). This potentially offers doctors more flexibility with the choice of chemotherapy, allowing them to base treatment, for example, on individual characteristics such as age and other medical conditions (e.g. kidney disease). It may also allow better patient management to help minimise side effects.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response: • Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers? • Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration • What is the impact of any disadvantages highlighted compared with current treatments
In current clinical practice, some people move from receiving pembrolizumab dosing every 3 weeks to pembrolizumab dosing every 6 weeks following completion of the chemotherapy treatment period. This is not currently anticipated to be an option with cemiplimab.

3i) Value and economic considerations

Introduction for patients: Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model. In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on: • The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?) • If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)? • How the condition, taking the new treatment compared with current treatments affects your quality of life.
In people with squamous disease, current practice is to give an immunotherapy called pembrolizumab in combination with a high dose (AUC6) of a chemotherapy called carboplatin; people with non-squamous disease are given pembrolizumab in combination with pemetrexed. Both of these chemotherapies are associated with significant toxicities and may not be suitable for all patients. Overall, the collective evidence from clinical trials, indirect treatment comparison versus pembrolizumab + chemotherapy, and clinical expert feedback provided to the company strongly suggests there are no clinically meaningful differences in outcomes between cemiplimab + chemotherapy and pembrolizumab + chemotherapy. However, in EMPOWER-Lung 3, cemiplimab could be initiated with a lower dose of carboplatin (AUC5) for people with squamous disease and could be combined with non-pemetrexed chemotherapy (paclitaxel + carboplatin) for people with non-squamous disease (4). This potentially offers doctors more flexibility with the choice of chemotherapy, allowing them to base treatment, for example, on individual characteristics such as their age and other medical conditions (e.g. kidney disease). It may also allow better patient management to help minimise side effects.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Regeneron provides an annual contribution of £30,000 to the Global Lung Cancer Coalition (GLCC) which is a loose coalition of registered charitable/not-for-profit organisations. Since the beginning of 2005, the GLCC has been administered by the Roy Castle Lung Cancer Foundation (RCLCF), a UK based charity (Registered in England & Wales, charity number: 03059425) and GLCC member. All corporate governance and financial structures of the GLCC are through the RCLCF and carried out under UK charity law. Regeneron's contribution to GLCC through the RCLCF is to broadly support the coalition's overall mission and annual workplans that carry our GLCC's commitment to "improving disease outcomes for all lung cancer patients."

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Regeneron is not aware of any potential equality issues that are relevant to this appraisal.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
European Public Assessment Report (European Medicines Agency): https://www.ema.europa.eu/en/documents/variation-report/libtayo-h-c-004844-ii-0028-epar-assessment-report-variation_en.pdf EMPOWER-Lung 3 trial: published papers (open access): • 1-year data (full population): https://www.nature.com/articles/s41591-022-01977-y • 2-year data (full population): https://www.jto.org/article/S1556-0864(23)00185-5/fulltext#%20 • 2-year data (MHRA label population): https://www.lungcancerjournal.info/article/S0169-5002(24)00355-6/fulltext • Quality of life data (full population): https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.34687 Cemiplimab summary of product characteristics and patient leaflet: https://www.medicines.org.uk/emc/product/10438/smpc#about-medicine https://www.medicines.org.uk/emc/product/10438/pil#gref Lung cancer educational materials: • Patient.info: https://patient.info/cancer/lung-cancer-leaflet • Cancer Research UK: https://www.cancerresearchuk.org/about-cancer/lung-cancer • NHS: https://www.nhs.uk/conditions/lung-cancer/ • Macmillan Cancer Support: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer NICE guidance for lung cancer diagnosis and management: https://www.nice.org.uk/guidance/ng122 Further information on NICE and the role of patients: • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-

content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

Alopecia – hair loss

Anaemia – a condition that develops when the body does not produce enough healthy red blood cells

Colitis – inflammation of the large intestine

Dyspnoea – shortness of breath

Locally advanced disease – disease that has spread to tissue or lymph nodes close to its original site, but has not yet reached other parts of the body

Lymph nodes – small bean-shaped structures that contain white blood cells, which fight infection

Metastatic disease – disease that has spread from its original site to other parts of the body

Nephritis – inflammation of the kidney

Non-squamous cell lung cancer – lung cancer that does not start in squamous cells. The most common types are adenocarcinoma and large cell cancer. Adenocarcinoma starts in epithelial cells, which are the cells in the lung that make mucus. Large cell cancer can start in any part of the lung.

PD-L1 – Programmed cell death ligand 1. A protein that is found on the surface of cancer cells. It can bind to immune cells and block the body's immune response, allowing the cancer to grow

Pneumonitis – inflammation of the lungs

Squamous cell lung cancer – a type of NSCLC that starts in squamous cells, which are the flat cells lining the inside of the airways in the lung

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. Global Cancer Observatory. GLOBOCAN 2022: United Kingdom. 2022.

2. Bristol Technology Assessment Group. Treatments for non-small-cell lung cancer [ID6234]: analysis plan. 2023.

3. Canadian Agency for Drugs and Technologies in Health. CADTH Reimbursement Review. Patient and clinician group input. Cemiplimab (Libtayo). 2023.

4. Gogishvili M, Melkadze T, Makharadze T, Giorgadze D, Dvorkin M, Penkov K, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. Nat Med. 2022;28(11):2374-80.

5. Makharadze T, Gogishvili M, Melkadze T, Baramidze A, Giorgadze D, Penkov K, et al. Cemiplimab Plus Chemotherapy Versus Chemotherapy Alone in Advanced NSCLC: 2-Year Follow-Up From the Phase 3 EMPOWER-Lung 3 Part 2 Trial. J Thorac Oncol. 2023;18(6):755-68.

6. Makharadze T, Quek RGW, Melkadze T, Gogishvili M, Ivanescu C, Giorgadze D, et al. Quality of life with cemiplimab plus chemotherapy for first-line treatment of advanced non-small cell lung cancer: Patient-reported outcomes from phase 3 EMPOWER-Lung 3. Cancer. 2023;129(14):2256-65.

7. Baramidze A, Makharadze T, Gogishvili M, Melkadze T, Giorgadze D, Penkov K, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer with PD-L1 ≥ 1 %: A subgroup analysis from the EMPOWER-Lung 3 part 2 trial. Lung Cancer. 2024;193:107821.

8. Makharadze T, Gogishvili M, Melkadze T, Baramidze A, Giorgadze D, Penkov K, et al. Erratum: In the published article titled "Cemiplimab Plus Chemotherapy Versus Chemotherapy Alone in Advanced NSCLC: 2-Year Follow-up From the Phase 3 EMPOWER-Lung 3 Part 2 Trial", J Thorac Oncol. 2023 Jun;18(6):755-768. J Thorac Oncol. 2023.

9. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2020;38(14):1505-17.

10. Paz-Ares L, Vicente D, Tafreshi A, Robinson A, Soto Parra H, Mazières J, et al. A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy in Patients With Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407. J Thorac Oncol. 2020;15(10):1657-69.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Regeneron response to EAG clarification questions

October 21st 2024

File name	Version	Contains confidential information	Date
ID3949 cemiplimab clarification questions to company [Redacted]_21OCT2024	1.0	Yes	21 Oct 2024

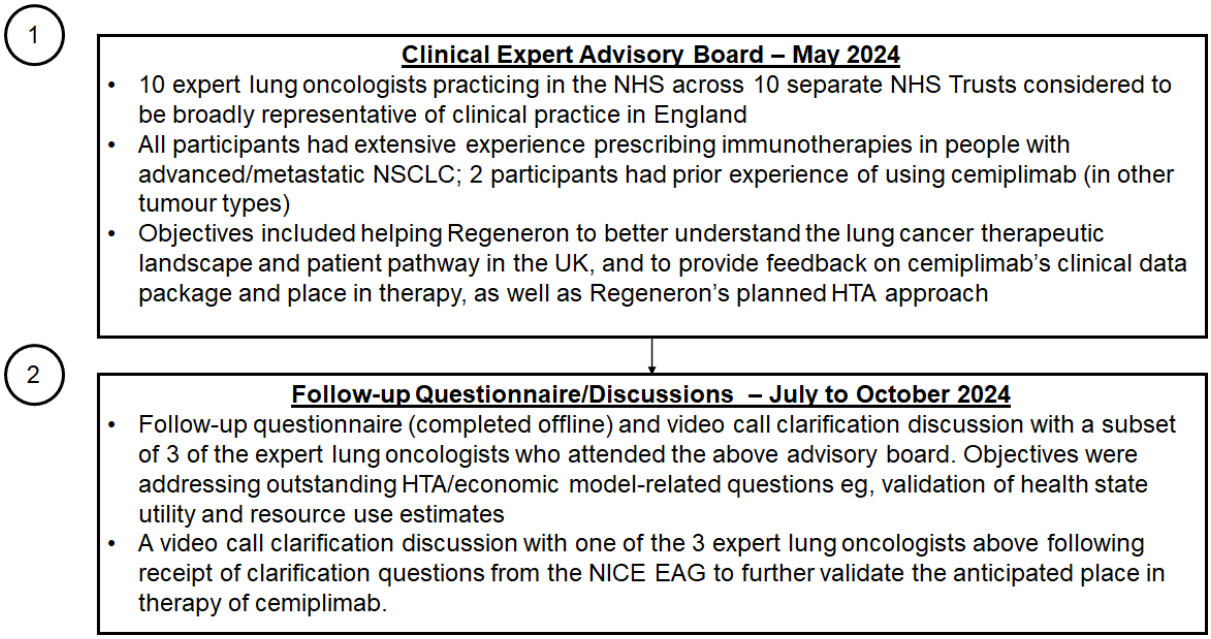
Section A: Clarification on effectiveness data

A1. The company justified various decisions within their submission based on consultation with clinical oncologists. Are the company able to provide the full minutes from these meetings with details supporting the decisions made for the decision problem, clinical effectiveness and cost-effectiveness?

Company response:

A summary of the approach for clinical expert feedback is shown below.

Summary of Clinical Expert Feedback Elicitation



EAG, Evidence Assessment Group; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; NSCLC, non-small-cell lung cancer

A report of the advisory board held in May 2024 is provided alongside this response (please see file called '*Data on file – NSCLC advisory board report*' in the 'Data on File' references folder). Following the advisory board, follow-up questions were sent to a subset of the participants and their responses were discussed during individual video clarification calls. A further video clarification was held with one of the participants following receipt of questions from the NICE EAG. Notes from these calls are provided alongside these clarification responses (see file called *'Data on file – NSCLC clinician follow-up'*).

Key excerpts from the ad-board report are given below:

Pembrolizumab + chemotherapy as the only relevant comparator

"There was consensus that pembrolizumab + chemotherapy is the most appropriate comparator" [page 12, Data on file – NSCLC advisory board report].

Modelling equivalent efficacy

"All advisors felt that efficacy data for cemiplimab and pembrolizumab looked similar, with no noticeable differences" [page 9, Data on file – NSCLC advisory board report].

"Advisors commented that there is no reason to think that cemiplimab would be any different to pembrolizumab. […] asked whether any advisors disagreed with this position, and nobody raised an objection" [page 12, Data on file – NSCLC advisory board report].

Inclusion of both squamous and non-squamous histologies in the economic base case

"Advisors agreed that for the purposes of a NICE submission, there is no rationale to split out different histologies and agreed that the modelled survival curves are unlikely to differ meaningfully based on histology or PD-L1 expression level group (1-49% vs ≥50%)" [page 12, Data on file – NSCLC advisory board report].

Use of long-term follow-up data for pembrolizumab + chemotherapy to inform modelling assumptions for cemiplimab + chemotherapy

"…advisors would be happy to assume that treatment benefit continues up to 5 years, and agreed that evidence on longer-term (e.g., 5-year) pembrolizumab + chemotherapy PFS/OS outcomes would be broadly generalizable to and appropriate for supporting assumptions about longer-term cemiplimab + chemotherapy PFS/OS outcomes" [page 13-14, Data on file – NSCLC advisory board report].

A2. Appendix D (p.64): Please can the company provide the full technical report for the Network Meta-Analyses: Regeneron UK Limited. *Data on file: Cemiplimab combination NMA report*. 2024.

Company response: The full NMA technical report is provided alongside this response (see file called *'Data on file – cemiplimab combination NMA report'* in the 'Data on File' references folder).

A3. Section A.5 (p.18): The company note that the clinical trial (EMPOWER-Lung 3) was stopped early on the recommendation of an independent data monitoring committee owing to superior overall survival. Please can the company provide a list of formal criteria that were used to stop this trial prematurely?

Company response: The trial was stopped at the second interim analysis. Timing of this analysis was pre-specified to occur when approximately 204 deaths (70% of total OS events) were observed (1). The Independent Data Monitoring Committee reviewed the results of this interim analysis based on a Lan-DeMets approach to the O'Brien-Fleming alpha-spending function and concluded that statistical significance was demonstrated for overall survival (OS). The committee recommended that the study be unblinded; the study was therefore stopped and the data were designated as the primary analysis. The alpha-spending functions used in the trial are shown in Table 1.

Table 1 Alpha-spending for analysis of overall survival in EMPOWER-Lung 3 (Part 2)

OS		**Value**
Interim analysis 1	Z	2.958
Deaths = ~146	Alpha (2-sided[a])	0.00310
Interim analysis 2	Z	2.465
Deaths = ~204	Alpha (2-sided[a])	0.01370
Final analysis	Z	2.002
Deaths = ~291	Alpha (2-sided)	0.04528

[a]As a two-sided test is used at interim, the superiority of cemiplimab treatment will be claimed if the statistical boundary is crossed

Source: Regeneron Pharmaceuticals Inc. Protocol R2810-ONC-16113; Statistical analysis plan v1.0 (April 17 2020); Section 7, Table 3 (available in the supplementary information to Gogishvili et al, 2022 (1))

A4. Priority question: Section A.4 (pp. 12-13): The company retained the same population as in the NICE scope in the decision problem. However, the company justified their decision to focus on one comparator from the NICE scope based on clinical differences between patients that are eligible to receive immunotherapy (IO) + chemotherapy versus other treatments. Please can the company confirm if this means that cemiplimab+ chemotherapy is only appropriate for a subset of the population defined by the NICE scope? Please define that population subset.

Company response: As described in the company submission, systemic therapy is the mainstay of treatment, and immunotherapy (IO) with or without platinum-based chemotherapy is available and routinely offered to all patients irrespective of histology or PD-L1 level unless contra-indicated. As use of chemotherapy alone in current clinical practice is generally limited to people who are contra-indicated to IO (and would also be contra-indicated for cemiplimab), chemotherapy was not considered a relevant comparator for this appraisal.

<u>PD-L1 1-49%</u>

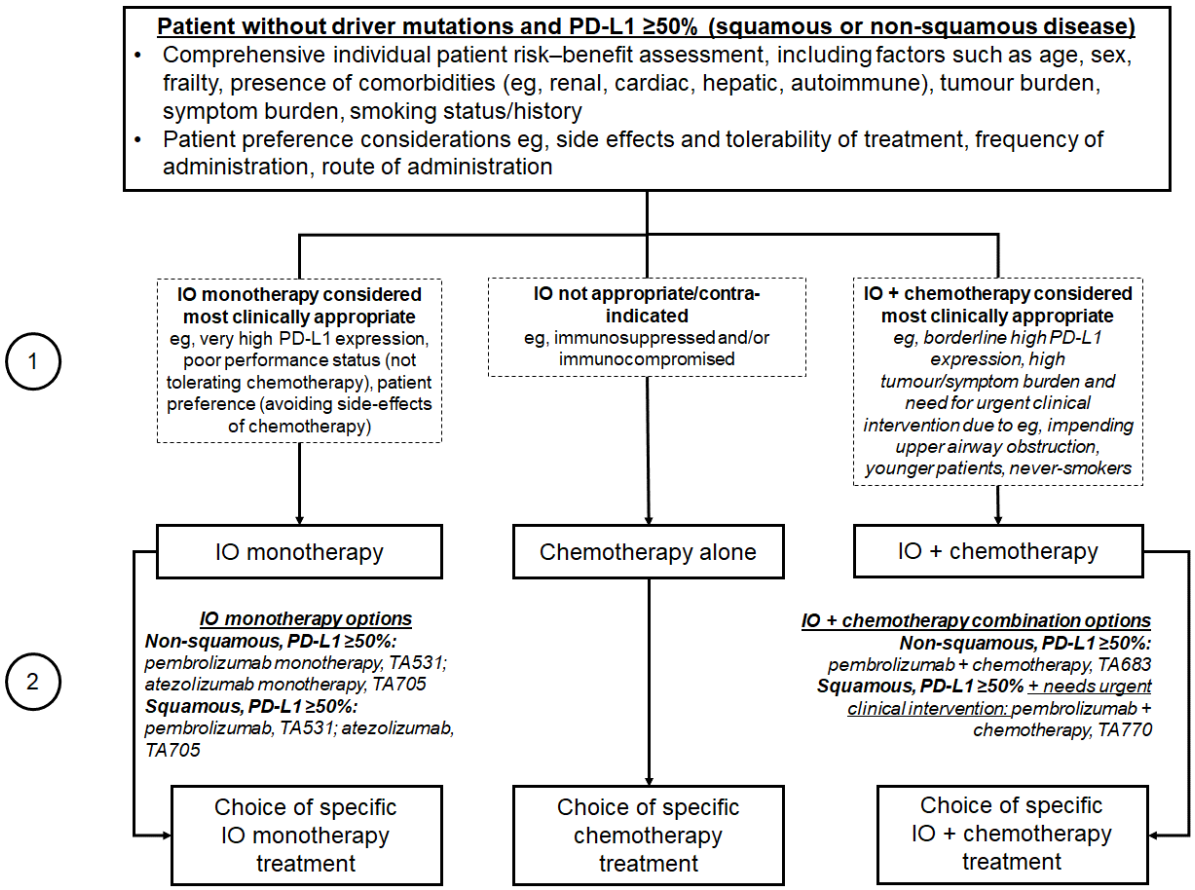
IO + chemotherapy is the only routinely available IO-based option for patients with PD-L1 levels 1-49% among those with squamous and non-squamous disease and is therefore standard of care and the only relevant comparator in this population.

<u>PD-L1 ≥50%</u>

For patients with PD-L1 ≥50%, both IO monotherapy and IO + chemotherapy are routinely available as treatment options and clinicians face more complex decision making.

The aim of combination treatment is for chemotherapy to help achieve a rapid response so the person can benefit from IO later (2). However, the addition of chemotherapy to an IO drug is associated with incremental toxicity, and a comprehensive risk–benefit assessment regarding the most suitable treatment modality is needed that takes into account heterogeneous patient characteristics (e.g., age and comorbidity burden), needs, and preferences.

Treatment Decision-making Schematic for Patients with PD-L1 ≥50% (both IO Monotherapy and IO + Chemotherapy Routinely Available)



IO, immunotherapy; PD-L1, programmed death-ligand 1

Pembrolizumab is by far the most frequently used IO in people with locally advanced or metastatic NSCLC for whom IO + chemotherapy is considered the most appropriate choice, with >80% of the current market share across histologies and PD-L1 levels ≥1% (based on 2023 CancerMPact market share data) (3). Cemiplimab + chemotherapy is therefore anticipated to be primarily used as an alternative to (i.e., displace use of) pembrolizumab + chemotherapy among people with PD-L1 expression ≥1%. The clinical expert lung oncologists who attended the advisory board described in the response to Question A1 confirmed that pembrolizumab + chemotherapy is the most appropriate comparator for this appraisal.

"There was consensus that pembrolizumab and chemotherapy is the most appropriate comparator" [page 12, Data on file – NSCLC advisory board report].

Therefore, cemiplimab should be made available to patients who fall within the scope of its label indication statement and who would otherwise be offered treatment with an IO + chemotherapy combination.

Cemiplimab target population

In combination with platinum-based chemotherapy for adults with untreated PD-L1-positive advanced/metastatic non-small-cell lung cancer (NSCLC) in people: • who have locally advanced NSCLC who are not candidates for definitive chemoradiation, or metastatic NSCLC. • whose tumours express PD-L1 (with at least a 1% tumour proportion score) and have no EGFR, ALK or ROS1 aberrations • who would otherwise be offered treatment with an IO + chemotherapy combination

A5. Priority question: Why was anti-PD-1 monotherapy not used as a comparator for patients with PD-L1>50%, particularly for people with squamous disease (the NICE treatment pathway for this population indicates that anti-PD-1 monotherapy would be the standard of care, and pembrolizumab+ chemotherapy would only be given if urgent clinical intervention is needed)?

Company response: As per the response to Question A4, for people with PD-L1 ≥50%, both IO monotherapy and IO + chemotherapy are available as treatment options and clinicians face more complex decision making. The aim of combination treatment is for chemotherapy to help achieve a rapid response so the person can benefit from IO later (2). However, the addition of chemotherapy to an IO drug is associated with incremental toxicity, necessitating comprehensive risk–benefit assessment regarding the most suitable treatment modality that takes into account heterogeneous patient characteristics (e.g., age and comorbidity burden), needs, and preferences.

Whilst the NICE recommendation for pembrolizumab + chemotherapy in people with squamous disease and PD-L1 ≥50% specifies that patients should “need urgent clinical intervention” (TA770), this is because the need for intervention with

combination therapy (e.g., impending major airway obstruction; squamous cell tumours often occur in the central part of the lung or primary airway) is considered, on balance, to outweigh the incremental toxicity burden compared with IO monotherapy (2, 4). The appraisal committee for TA770 were ultimately satisfied that while some patients with squamous disease and PD-L1 ≥50% may be considered more appropriate for IO monotherapy in clinical practice, those in need of urgent clinical intervention "*did benefit from*" IO + chemotherapy, and that this was an appropriate population in which to recommend pembrolizumab + chemotherapy (2). Similarly, it is anticipated that cemiplimab + chemotherapy would also be used in patients who need urgent clinical intervention on the basis of individual patient risk-benefit assessment and is therefore anticipated to be used as an alternative to (i.e., displace use of) pembrolizumab + chemotherapy among people with squamous disease and PD-L1 ≥50%.

The important role of IO + chemotherapy combination therapy in people with PD-L1 ≥50% is underscored by contemporary evidence-based guidelines. For example, NCCN include both IO monotherapies and IO + chemotherapy combination options as preferred (category 1) options in this patient group (5). Similarly, ESMO guidelines highlight the lack of head-to-head comparisons for IO monotherapy vs. IO + chemotherapy, the lack of validated biomarkers to select patients for either treatment modality, and also recommend IO + chemotherapy combinations as appropriate options for people with PD-L1 ≥50% (6).

A6. Section B.2.5 (p.48): The company note that the study was powered to the ITT population (PD-L1 any level), rather than the MHRA label population (PD-L1 ≥ 1%). In the risk of bias assessment, they report that groups were similar at the outset of the trial in terms of prognostic factors. Can the company confirm if similarity of prognostic factors at baseline was considered in the MHRA label population as well as the ITT population, particularly with regards to sex and ECOG PS?

Company response: Baseline demographics and disease characteristics for both the ITT and MHRA label populations were presented in our submission (Document B, Table 6).

The EMA stated in the EPAR for cemiplimab + chemotherapy in NSCLC that the baseline demographics and disease characteristics for the MHRA label population were *"equivalent to the ITT population"* (7). As per the ITT population, baseline demographics and disease characteristics were generally well balanced between the two treatment arms in the MHRA label population, including with regards to factors such as sex and ECOG PS (≤ 5% difference between treatment arms) (8)

A7. Appendix D (p. 101): The numbers of patients with locally advanced (stage III) and metastatic (stage IV) disease in the non-squamous, PD-L1 ≥ 50% group do not correspond to the numbers in the column headers and the percentages do not add up to 100% (e.g., 12 (13.8%) patients are reported as having metastatic (stage IV) disease, and 9 (10.3 %) are reported as having locally advanced (stage III) disease). Please can the company explain these disparities?

Company response: We apologise for this typographical error in Table 92 of the original submission and thank the EAG for bringing it to our attention. In the non-squamous, PD-L1 ≥50% group, all of the values for metastatic (stage IV) disease are incorrect. A corrected version of the table is given below.

Table 2 Baseline characteristics: non-squamous histology NICE decision problem subgroups (corrected version of Table 92 from Appendix E in the original submission)

	Non-squamous, PD-L1 1-49%			Non-squamous, PD-L1 ≥50%		
	Cemiplimab + chemo (n = 61)	**Placebo + chemo (n = 33)**	**Total (n = 94)**	**Cemiplimab + chemo (n = 61)**	**Placebo + chemo (n = 26)**	**Total (n = 87)**
Age, years						
Median (IQR)	61.0 (54.0; 67.0)	59.0 (52.0; 66.0)	61.0 (53.0; 66.0)	63.0 (57.0; 68.0)	63.5 (55.0; 70.0)	63.0 (55.0; 68.0)
≥65 years, n (%)	23 (37.7)	9 (27.3)	32 (34.0)	26 (42.6)	10 (38.5)	36 (41.4)
Sex, n (%)						
Female	14 (23.0)	8 (24.2)	22 (23.4)	10 (16.4)	7 (26.9)	17 (19.5)
Male	47 (77.0)	25 (75.8)	72 (76.6)	51 (83.6)	19 (73.1)	70 (80.5)
Geographic region, n (%)						
Europe	47 (77.0)	29 (87.9)	76 (80.9)	48 (78.7)	22 (84.6)	70 (80.5)
Asia	14 (23.0)	4 (12.1)	18 (19.1)	13 (21.3)	4 (15.4)	17 (19.5)
Race, n (%)						
White	47 (77.0)	29 (87.9)	76 (80.9)	48 (78.7)	22 (84.6)	70 (80.5)
Asian	14 (23.0)	4 (12.1)	18 (19.1)	13 (21.3)	4 (15.4)	17 (19.5)
ECOG PS, n (%)						
0	14 (23.0)	8 (24.2)	22 (23.4)	19 (31.1)	5 (19.2)	24 (27.6)
1	47 (77.0)	24 (72.7)	71 (75.5)	42 (68.9)	21 (80.8)	63 (72.4
Missing	0	1 (3.0)	1 (1.1)	0	0	0
Brain metastases, n (%)	5 (8.2)	3 (9.1)	8 (8.5)	9 (14.8)	3 (11.5)	12 (13.8)
Cancer stage at screening, n (%)						
Metastatic	54 (88.5)	28 (84.8)	82 (87.2)	54 (88.5)	24 (92.3)	78 (89.7)
Locally advanced	7 (11.5)	5 (15.2)	12 (12.8)	7 (11.5)	2 (7.7)	9 (10.3)

Smoking history, n (%)						
Current smoker	29 (47.5)	16 (48.5)	45 (47.9)	25 (41.0)	9 (34.6)	34 (39.1)
Past smoker	20 (32.8)	13 (39.4)	33 (35.1)	27 (44.3)	11 (42.3)	38 (43.7)
Never smoker	12 (19.7)	4 (12.1)	16 (17.0)	9 (14.8)	6 (23.1)	15 (17.2)

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD-L1, Programmed cell death ligand 1; PS, performance status

Source: Regeneron data on file (NICE subgroup demographics) (9)

A8. Section B.2.9 (p.61): The company note that "The safety NMA (e.g., Grade 3–5 AEs, IMAEs, DAEs) showed results with wide credible intervals and limited significance". Are there any specific adverse events that the company would single out as being most important and prevalent, and whether there are any of these appear to be more likely for cemiplimab or pembrolizumab?

Company response: Individual AEs were not included in the NMA; the three safety outcomes were Grade 3 to 5 AEs, immune-mediated AEs, and discontinuation due to AEs. As rates of specific individual AEs were not reported for the comparator in a like-for-like population (i.e., any histology, PD-L1 >1%) it was not considered appropriate to include specific AEs in the analysis.

One of the clinical expert lung oncologists consulted by Regeneron (Question A1) confirmed that based on the current evidence base and extensive UK clinical experience with a range of IOs in NSCLC, and consistent with prior NICE appraisals, there is *"widespread belief/understanding that cemiplimab would have a very similar safety profile to pembrolizumab in NSCLC"* (10). For example, in a previous technology appraisal in NSCLC (TA705), clinical experts highlighted that there were "*no robust differences in toxicity or efficacy*" between the different NSCLC IO options under assessment (11).

A9. EMPOWER-Lung 3 protocol (p.27): In the clinical trial (EMPOWER-Lung 3) protocol, the company noted that they would focus on patients whose tumours express PD-L1 in 1% to <50% of tumour cells and that the overall population in the trial would include patients whose tumours express PD-L1 in <50% of tumour cells. The company justified this as follows: '*anti-PD-1 monotherapy has been shown to be efficacious in NSCLC patients whose tumors express PD-L1 in ≥50% of tumor cells but not in patients whose tumors express PD-L1 in <50% of tumor cells… In order to treat patients whose tumors express lower levels of PD-L1, a combination immunotherapy regimen will be required*'. Please can the company explain why the scope was expanded to include patients with PD-L1>50%?

Company response: EMPOWER-Lung 3 was originally designed as a phase 3 randomised, 3-arm study of standard of care chemotherapy vs. cemiplimab +

chemotherapy vs. cemiplimab + ipilimumab + chemotherapy in patients with PD-L1 <50%. In EMPOWER-Lung 3 part 1, 323 patients with PD-L1 expression of <50% were randomised (1:1:1) to: standard platinum-based doublet chemotherapy for 4 cycles, cemiplimab 350 mg once every 3 weeks for up to 108 weeks + standard chemotherapy, or cemiplimab 350 mg every 3 weeks for up to 108 weeks + reduced chemotherapy for 2 cycles + ipilimumab 50 mg every 6 weeks for up to 4 cycles.

Protocol Amendment #4 was implemented on Jan 18th, 2019, which added the Part 2 study design. Part 2 was designed to demonstrate the benefit of adding cemiplimab to chemotherapy regardless of PD-L1 expression level. The rationale for this amendment was the following:

- Changing treatment landscape: KEYNOTE studies 189 and 407 were FDA approved in August 2018 and October 2018 respectively.
- Emerging data from MYSTIC and Checkmate 227 showed that the addition of a CTLA-4 inhibitor (e.g., ipilimumab) to a PD-1 or PD-L1 inhibitor did not meaningfully improve efficacy in combination therapy but was associated with incremental toxicity.

Part 2 of the EMPOWER-Lung 3 study was ultimately considered by EMA (and subsequently MHRA) to an appropriate basis for which to approve cemiplimab + chemotherapy as an option for all indicated patients with PD-L1 expression ≥1%, including both those with PD-L1 1-49% and those with ≥50%.

A10. Appendix D: Please can the company provide the following: a protocol for the systematic literature reviews, an explanation of how the data extraction forms were developed and a list of items that were included in the data extraction forms?

Company response: Copies of the clinical SLR protocol and SLR report are provided alongside these clarification responses. Relevant content from these materials on the approach for data extraction can also be found in Appendix 1 of this response.

A11. Similarity of cemiplimab and pembrolizumab:

- **Could you please clarify why clinical experts thought that there would unlikely be a difference in effectiveness and adverse events between cemiplimab and pembrolizumab (page 61)?**

Company response: Cemiplimab and pembrolizumab have the same mode of action and robust published evidence suggesting meaningful differences in effectiveness or safety outcomes between the two agents is lacking. The feedback from the participants at the advisory board and involved in subsequent follow-up discussions (Question A1) was based on their interpretation of the current evidence base and extensive clinical experience with a range of IOs in NSCLC and other tumour types. This is consistent with previous NICE appraisals, where clinical experts have indicated that they would expect no meaningful differences in effectiveness or safety between the different IOs in NSCLC. For example, the FAD for TA705 highlights clinical expert opinion that there are *"no robust differences in toxicity or efficacy"* between the different NSCLC IO options under assessment (11).

Contemporary evidence-based guidelines also support the view that there are unlikely to be meaningful differences in outcomes associated cemiplimab vs. pembrolizumab. Cemiplimab + chemotherapy is the only IO + chemotherapy combination other than pembrolizumab + chemotherapy that has a 'preferred' (category 1) NCCN guidelines recommendation for the treatment of patients with advanced/metastatic NSCLC (5). The NCCN has also assigned both options a score of 4 out of 5 ('very effective') for efficacy across histology and PD-L1 subgroups in its Evidence Blocks™ assessment. This assessment considers both published trial evidence and real-world clinical experience of the panel members in more diverse real-world settings. NCCN has also assigned all recommended IO monotherapy options a score of 4 out of 5 ('very effective') for efficacy where it is recommended as an option (PD-L1 ≥50%, any histology) in its Evidence Blocks™ assessment, suggesting there are not meaningful intrinsic differences in the effectiveness of different IO agents in this population. In addition, the most recent European Society for Medical Oncology (ESMO) guidelines for metastatic NSCLC include cemiplimab + chemotherapy as an alternative to other IO + chemotherapy combinations (6). Based on the key registrational trials for cemiplimab + chemotherapy and

pembrolizumab + chemotherapy in advanced/metastatic NSCLC, ESMO has scored both as 4 (indicating high clinical benefit) on the ESMO-Magnitude of Clinical Benefit Scale (12).

Furthermore, in a recent study on pharmacological class effects of anticancer drugs and opportunities for decreasing healthcare spending, Goldstein et al (2024) highlighted that most trials using various PD-1 immunotherapies in comparable clinical contexts have yielded similar outcomes in NSCLC, supporting a class effect (13). The few exceptions are attributed to minor differences in trial design and execution, or statistical variations expected upon repetition, with significant differences in efficacy considered unlikely. According to Goldstein et al (2024), interchangeability between members of a class of anti-cancer drugs could allow for cost savings and improved access to treatment (13).

- **What is the difference between cemiplimab and pembrolizumab that enables greater flexibility in use of the adjunct chemotherapy with cemiplimab compared to pembrolizumab (pages 18/19)? Is there any reason why this difference may result in different effectiveness and adverse event outcomes for cemiplimab + chemotherapy versus pembrolizumab versus chemotherapy?**

Company response: There is no intrinsic difference between cemiplimab and pembrolizumab that affects which chemotherapies can be used in combination with them. The chemotherapy options included in Blueteq protocols (i.e., NHS England commissioning policy) for use with pembrolizumab are based on the chemotherapy treatment protocols used in the registrational KEYNOTE RCTs (KEYNOTE-189 and KEYNOTE-407) (14):

- AUC6 carboplatin for people with squamous disease
- Pemetrexed-containing regimens for people with non-squamous disease.

We anticipate that NHS England commissioning policy for cemiplimab + chemotherapy would similarly be aligned with the flexible, investigator's-choice chemotherapy treatment protocols permitted in the registrational EMPOWER-Lung 3 RCT. As there was greater flexibility in EMPOWER-Lung 3 compared with the KEYNOTE studies regarding the starting dose of carboplatin (both AUC6 and AUC5

dosing was allowed) and the use of pemetrexed-free regimens (with paclitaxel as an alternative), we expect that this will be reflected in the Blueteq protocol for cemiplimab + chemotherapy. This will give clinicians the option to initiate treatment in people with squamous disease with carboplatin at a lower dose (i.e., AUC5 instead of AUC6), and to use an alternative to pemetrexed (i.e., paclitaxel) in people with non-squamous disease, meaning that they have greater flexibility to tailor treatment according to patients' individual characteristics (e.g., age and comorbidity burden), needs, and preferences.

AUC5 vs AUC6 carboplatin (squamous)

Feedback from clinical expert lung oncologists practicing in the NHS (Question A1) was that the ability to initiate carboplatin at a dose of AUC5 would be "useful" and "helpful" and could be anticipated to lead to a reduction in the incidence/severity of dose-related carboplatin toxicities such neutropenia, thrombocytopenia and peripheral neuropathy, which can have a substantial impact on patients' quality of life.

It is well documented that carboplatin-associated bone marrow suppression (e.g., neutropenia and thrombocytopenia) is dose-dependent and is also the primary dose-limiting toxicity of carboplatin (15). Neutropenia significantly increases the risk of infections due to reduced immune response and can lead to febrile neutropenia necessitating hospitalisation (16). Thrombocytopenia can lead to severe bleeding complications (particularly when platelet counts drop below 50 x 10^9/L) including gastrointestinal bleeding and haemorrhagic strokes, which can be life-threatening (17). Patients may also require delays in chemotherapy administration to manage thrombocytopenia, and severe cases may necessitate platelet transfusions, further complicating treatment (16). Peripheral neuropathy is also dose-dependent and the risk of carboplatin-induced peripheral neuropathy is higher in patients aged >65 years and in those previously treated with neurotoxic agents (18).

As described in the company submission (Document B, Figure 3), approximately [redacted] of patients with squamous histology randomised to the cemiplimab + chemotherapy arm who received a carboplatin-containing chemotherapy regimen in EMPOWER-Lung 3 were selected, based on investigator's choice, to receive

carboplatin at a lower starting dose of AUC5 (19), providing further evidence on the value of carboplatin dosing flexibility.

Without access to more flexible, evidence-based IO + chemotherapy treatment protocols, people with squamous disease remain at avoidably high risk of dose-related carboplatin toxicities, which not only represent a high burden to patients, but substantial costs to the NHS.

Paclitaxel vs pemetrexed (non-squamous)

Paclitaxel and pemetrexed have unique safety/toxicity profiles, and clinical expert feedback suggested that the risk of renal toxicity, for example, would be anticipated to be lower with paclitaxel compared with pemetrexed. These different chemotherapy agent toxicity profiles are consistent with post-hoc safety data from EMPOWER-Lung 3 (Table 3).

Alternatives to pemetrexed may be particularly important for patients with renal dysfunction (eGFR < 60 mL/minute), which affects more than 15% of patients with lung cancer (20). These patients could benefit from availability of a pemetrexed-free IO + chemotherapy regimen, as renal toxicity can place an immediate burden on patients and may be sustained after treatment stops, thereby jeopardising subsequent lines of treatment.

Pemetrexed is also to be used with caution in patients with large fluid collections such as pleural effusions and ascites, and about 40% of lung cancer patients develop pleural effusions throughout their treatment course (21). Hence, clinicians are advised to consider drainage of third space fluid collection prior to treatment with pemetrexed (22), and such patients could similarly potentially benefit from availability of a pemetrexed-free IO + chemotherapy regimen.

Table 3 EMPOWER-Lung 3 post-hoc analysis of TEAEs for patients randomised to cemiplimab + chemotherapy and treated with pemetrexed versus paclitaxel-containing chemotherapy regimens (non-squamous histology)

Event, n (%) of patients	Pemetrexed (n = 114)		Paclitaxel (n = 39)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs in ≥10% of patients (either group)				
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
WBC count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]
Amylase increased	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; WBC, white blood cell

Source: Regeneron data on file: pemetrexed vs paclitaxel (23)

As per the lack of flexibility with current initial carboplatin dosing for people with squamous disease, without access to more flexible, evidence-based IO + chemotherapy treatment protocols that include alternatives to pemetrexed, people with non-squamous disease who could be more suitable to receive an alternative to pemetrexed remain at avoidably high risk of pemetrexed-associated toxicity.

Section B: Clarification on cost-effectiveness data

B1. Section B.3.2.2, page 100: The company state that subgroup analysis by cancer stage (locally advanced vs. metastatic) and by newly diagnosed vs recurrent after surgery metastatic disease were not conducted despite being in the NICE scope, as *"UK clinical expert lung oncologists did not consider that clinical effectiveness would differ"*. Are the company able to provide the full minutes from these meetings with details supporting this decision?

Company response: Feedback from UK clinical expert lung oncologists suggested that neither clinical outcomes nor costs are expected to be meaningfully different for patients with locally advanced disease (not eligible for definitive chemoradiation) versus metastatic disease, or for people who have undergone prior surgery for NSCLC versus those who have not. As stated in our response to Question A1, the advisory board report was included in the original submission pack (please see file called *'Data on file – NSCLC advisory board report'* in the 'Regeneron Data on File References' folder). We have provided notes from meetings with individual clinical advisors alongside these clarification responses.

As described in Table 1 of the submission (Document B), the Blueteq protocol (i.e. NHS England commissioning policy) permits treatment of patients with locally advanced NSCLC who are not candidates for definitive chemoradiation with pembrolizumab, despite pembrolizumab not having a UK marketing authorisation in locally advanced disease (14). According to clinical experts, Stage IIIb/c disease is considered "*de facto* metastatic" with the difference being primarily the anatomical site of the disease rather than prognosis (10).These patients are therefore managed in the same way as those with metastatic disease, and subgroup analysis by disease stage lacks relevance to UK clinical practice and treatment decisions. Feedback from UK clinical expert lung oncologists suggested that neither clinical outcomes nor costs are expected to be meaningfully different for patients with locally advanced disease (not eligible for definitive chemoradiation) versus metastatic disease, or for people who have undergone prior surgery for NSCLC versus those who have not. Although subgroup analysis by disease stage was planned in the overall population of the EMPOWER-Lung 3 RCT, the small number of patients in the study who were in the

licensed population (i.e., PD-L1 ≥1%) with locally advanced NSCLC precludes robust subgroup analysis.

Similarly, clinical expert feedback on the relevance of subgroup analysis according to whether patients had recurrent disease following prior surgery or were newly diagnosed with NSCLC was that "*the disease kinetics including responsiveness to systemic therapy is not determined or altered by previous surgery but by the biology of the disease.*"

B2. Section 3.3.1.2, page 106: The company state that the base case model selection for the survival analysis extrapolations was guided by UK clinical expert lung oncologists at an Advisory Board Meeting (24th May 2024). Please can the company provide the full minutes from this advisory board meeting and the responses to the follow-up questionnaire distributed to the advisory board to elicit further feedback?

Company response: As stated in our response to Question A1, the advisory board report was included in the original submission pack (please see file called *'Data on file – NSCLC advisory board report'* in the 'Regeneron Data on File References' folder). We have provided notes from meetings with individual clinical experts alongside these clarification responses.

Relevant excerpts from the advisory board report regarding choice of model for the base-case are given below:

"All advisors felt comfortable with the log-logistic model for 2-year PFS (21.5%) for cemiplimab + chemotherapy" [page 12, Data on file – NSCLC advisory board report].

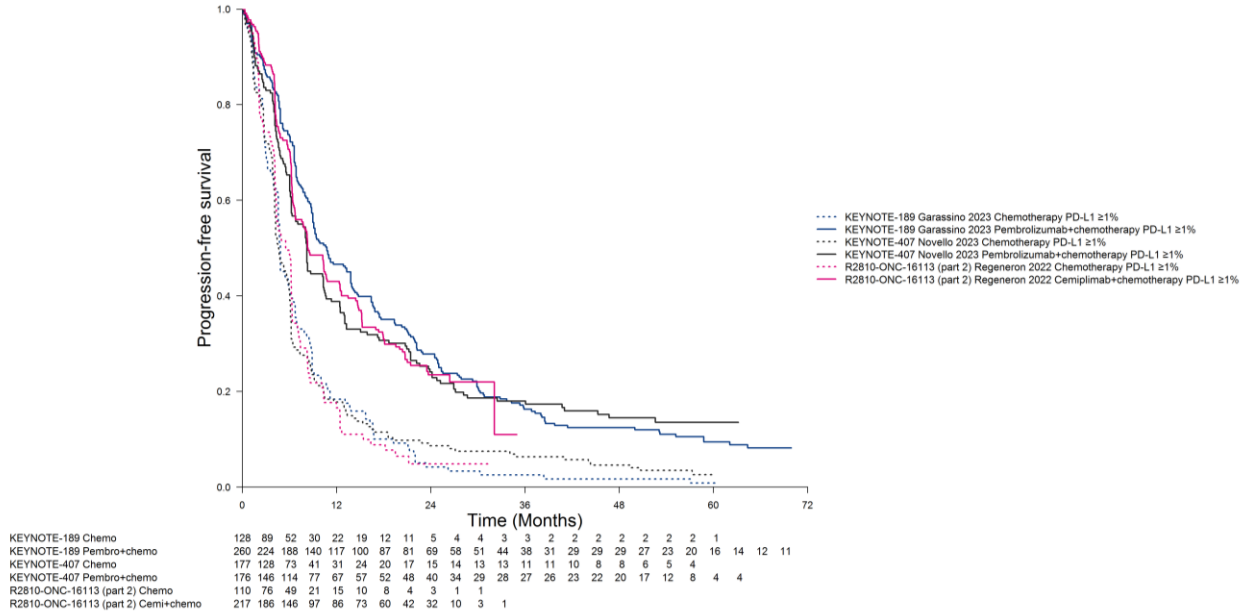
"Advisors agreed that around 10% OS at 10 years for cemiplimab combination would be clinically plausible. They ruled out all models other than log-logistic and log-normal, and recommended Regeneron use the more conservative log-logistic model for all modelled interventions" [page 12, Data on file – NSCLC advisory board report].

B3. Priority question: Section B.3.3.3, page 131: The company state that *"In the base case analysis, treatment benefit was assumed to continue to five years".* Please could the company comment further on the plausibility of the patients continuing to benefit to the same extent for three years following the two-year treatment period? What is the evidence that supports this assumption? Is there any reason to believe the duration of treatment benefit would differ between cemiplimab + chemotherapy and pembrolizumab + chemotherapy?

Company response: The evidence base as summarised in the company submission suggests there are no meaningful differences in clinical efficacy between cemiplimab + chemotherapy and pembrolizumab + chemotherapy. In the base case time-varying hazard ratio (HR) network meta-analysis (NMA) for patients with PD-L1 ≥1% and any histology (Document B, Section B.2.9.2.1), the point estimates were close to 1 with 95% credible intervals spanning 1 at all timepoints, indicating comparable efficacy with no statistically significant differences between cemiplimab + chemotherapy vs pembrolizumab + chemotherapy for both progression-free survival (PFS) and OS.

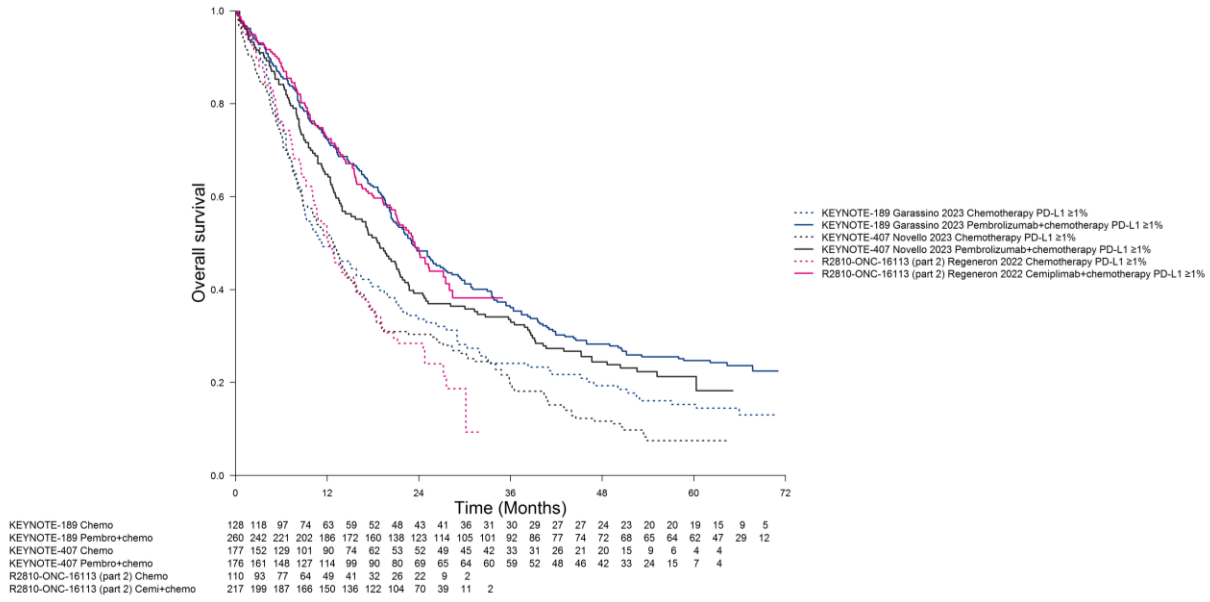
PFS and OS for EMPOWER-Lung 3 and KEYNOTE-189 or -407 studies are presented in Figure 1 and Figure 2, respectively. At present, EMPOWER-Lung 3 only has 2-year follow-up data available, whereas 5-year follow-up data are available for the registrational pembrolizumab + chemotherapy KEYNOTE studies. The figures demonstrate a highly similar survival trend for cemiplimab + chemotherapy and pembrolizumab + chemotherapy for both PFS and OS.

Figure 1 Progression-free survival Kaplan-Meier curves for patients with PD-L1 ≥1% and any histology



PD-L1, programmed death ligand 1.

Figure 2 Overall survival Kaplan-Meier curves for patients with PD-L1 ≥1% and any histology



PD-L1, programmed death ligand 1.

Both cemiplimab and pembrolizumab have a 24-month treatment stopping rule applied in the EMPOWER-Lung 3 and KEYNOTE-189 or -407 studies. In the NICE appraisals for pembrolizumab + chemotherapy (TA683 and TA770), the continuation of treatment effect after treatment stopping at 24 months was discussed (2, 24). In TA683, the committee accepted a treatment waning from three to five years after treatment initiation, while in TA770, the committee accepted a treatment effect

lasting to five years based on five-year follow-up from KEYNOTE-407. This suggests that duration of treatment benefit seen after five years for pembrolizumab + chemotherapy is expected to also be observed for cemiplimab + chemotherapy when longer follow-up becomes available. Cemiplimab + chemotherapy is also the only IO + chemotherapy combination other than pembrolizumab + chemotherapy that has a 'preferred' NCCN guidelines recommendation for the treatment of patients with advanced/metastatic NSCLC (5). NCCN has assigned both options a score of 4 out of 5 ('very effective') for efficacy across histology and PD-L1 expression level subgroups in its Evidence Blocks™ assessment, which is based on both published trial evidence and real-world clinical experience of the panel members in more diverse real-world settings, further supporting the assumption of similar treatment benefit.

Given the similar efficacy between cemiplimab + chemotherapy and pembrolizumab + chemotherapy and considering both IOs are subject to similar stopping rules, there is no reason to believe the duration of treatment benefit would differ between cemiplimab + chemotherapy and pembrolizumab + chemotherapy. Therefore, the same assumption as adopted in TA770 (treatment effect lasting five years) was applied in the current submission.

This assumption was validated at the previously described advisory board (Question A1) by clinical expert lung oncologists practicing in the NHS who confirmed that patients continue to benefit following two years of IO treatment. The participants did not perceive any meaningful differences in efficacy data between EMPOWER-Lung 3 and KEYNOTE-189 or -407 studies and confirmed that in the absence of longer-term follow-up data from EMPOWER-Lung 3, it is reasonable and appropriate to assume the same duration of treatment benefit for cemiplimab and pembrolizumab based on the longer-term follow-up reported for the KEYNOTE studies. The relevant excerpt from the advisory board report regarding the duration of treatment benefit assumption for the base-case is provided below:

"…advisors would be happy to assume that treatment benefit continues up to 5 years, and agreed that evidence on longer-term (e.g. 5-year) pembrolizumab + chemotherapy PFS/OS outcomes would be broadly generalizable to and appropriate

for supporting assumptions about longer-term cemiplimab + chemotherapy PFS/OS outcomes" [page 13-14, Data on file – NSCLC advisory board report].

B4. Section B.3.3.4, Page 135: Please could the company provide an additional sensitivity analysis using the safety data from the MHRA label population rather than the ITT population?

Company response: As far as Regeneron is aware, safety data for pembrolizumab + chemotherapy have not been reported for the equivalent of the cemiplimab MHRA label population, i.e. any histology, PD-L1 ≥1%. It is therefore not feasible to produce an NMA sensitivity analysis of safety data for cemiplimab + chemotherapy vs. pembrolizumab + chemotherapy in this population. As primary difference between the ITT population and the MHRA label population is the PD-L1 expression levels, no differences in safety profile are anticipated.

B5. Section 3.4.3, Page 140: Please could the company provide the full regression output from the linear fixed effects mapping models used to estimate the utility values for PFS and OS in the CEM?

Company response: The linear mixed effects model used to estimate the health state utility values included tumour response as a three-level covariate (progressor, progression-free responder, or progression-free non-responder), time since randomisation in weeks, an interaction term between time and tumour response, and a random intercept term to account for subject-specific effects.

The coefficients from the final model are summarized in Table 4.

The health state utilities in the CEM were estimated with the individual patient data (IPD) by predicting values for 1,000 random subjects using the regression coefficients, and the standard error was estimated by bootstrapping. Estimates of utilities for the progression-free patient group were generated by taking a weighted average of the two responder categories (progression-free responder, progression-free non-responder), with the weighting based on trial proportions of responders, regardless of treatment.

Table 4 EMPOWER-Lung 3 mixed effects model for health state utilities (EQ-5D 3L, UK tariff)

Coefficient	Estimate	Standard error	p-value
Intercept	0.7438	0.0067	<0.001
Time since randomization (weeks)	0.0007	0.0002	0.002
Response status [progression-free responders vs. progression-free non-responders]	0.0243	0.0064	<0.001
Response status [progressed vs. progression-free non-responders]	-0.0448	0.0124	<0.001
Time x response interaction [progression-free responders vs. progression-free non-responders]	-0.0006	0.0002	0.008
Time x response interaction [progressed vs. progression-free non-responders]	0.0003	0.0003	0.290

3L, three level; UK, United Kingdom.

B6. Priority question: Section 3.5.1, page 160: In the base-case it is assumed that ToT was equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. Please could the company comment further on the plausibility of this assumption given the differences in the estimated hazard ratios for treatment discontinuation for cemiplimab + chemotherapy and pembrolizumab + chemotherapy (Table 53, page 162)?

Company response: The EMPOWER-Lung 3 protocol allowed patients to continue treatment beyond the initial RECIST 1.1-defined progressive disease if the investigator perceived the patient to be experiencing clinical benefit or for other protocol defined reasons (see supplementary information to Gogishvili et al 2022 (1)). However, the MHRA label for cemiplimab specifies that cemiplimab treatment "may be continued until disease progression or unacceptable toxicity" (25). Based on the MHRA label and the opinion of UK clinical expert lung oncologists, it is not anticipated that treatment with cemiplimab would continue beyond progression in clinical practice, as it did in the clinical trial for some patients. As such, the assumption that time on treatment (ToT) was equal to PFS was used in the base case.

For EMPOWER-Lung 3, the difference between ToT and PFS was explored in a scenario analysis through the application of a HR to the PFS curve, with the HR estimated by means of a Cox model. Note the underlying assumption of independence of groups is violated, as patients are included in each 'group' defined

by the outcome (i.e., PFS and time to discontinuation [TTD]), so the HR should be interpreted with caution.

For pembrolizumab + chemotherapy, there was no publicly available time-to-event data for ToT. For pembrolizumab + chemotherapy, a HR was crudely estimated from the median PFS and median ToT reported in the KEYNOTE studies where a publication reported both median PFS and ToT from the same data cut.

- KEYNOTE-407 (14.3 months of follow-up) reported a median PFS of 8 months and a median ToT of 7.1 months (26).
- KEYNOTE-189 (31 months of follow-up) reported a median PFS of 9 months and a median ToT of 7.2 months (27).
- Hazards were estimated from the medians using an exponential distribution and HRs were calculated and weighted by split of squamous and non-squamous patients in EMPOWER-Lung 3. This is a crude approach to estimate the differences between ToT and PFS for pembrolizumab + chemotherapy and should be interpreted with caution.

Although the estimated HRs differed (Table 53 of the company submission), given the similarity in the mechanism of action of the treatments, efficacy (see results of the NMA and Figure 1 and Figure 2 in this response), and safety (see results of the NMA), there is no reason to believe the duration of treatment would differ between cemiplimab + chemotherapy and pembrolizumab + chemotherapy in clinical practice. Clinical experts supported this assumption; at the aforementioned advisory board (Question A1) numerical differences in the discontinuation rates between EMPOWER-Lung 3 and KEYNOTE-189 or -407 studies were noted, but participants were cautious about drawing conclusions based on cross-trial comparisons with differences potentially owing to immunotherapy experience bias (i.e., less familiarity/experience with immunotherapies during earlier KEYNOTE studies potentially driving higher discontinuation rates).

Overall, modelling ToT by assuming it was equal to PFS was deemed to be most appropriate for the base-case analysis. The estimated HRs were explored in a scenario analysis (scenario 4) with cemiplimab + chemotherapy remaining dominant

vs. pembrolizumab + chemotherapy, despite the decreased total treatment costs for pembrolizumab + chemotherapy in this scenario (Table 5).

Table 5 Scenario analysis: applying HRs to PFS to estimate time on treatment (PD-L1 ≥1%, any histology)

	Total			Incremental			ICER (£/QALY)
	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	
Base case (PD-L1 ≥1% and any histology), two-step NMA (log-logistic PFS and OS)							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	126,144	2.93	2.15				
Scenario 4: Applying HRs to PFS to estimate time on treatment							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	[redacted]	0.33	[redacted]	Dominant
Pembro + chemo	116,751	2.93	2.15				

HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life year; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; pembro + chemo, pembrolizumab + chemotherapy

B7. Section B.3.8.4, Page 181: The company note that: "The PD-L1 ≥50%, squamous histology subgroup resulted in an ICER indicating that cemiplimab + chemotherapy was less costly and less effective than pembrolizumab + chemotherapy". This is likely due to a slightly worse effectiveness estimate in this subgroup, although there may be considerable uncertainty in the estimate. Can the company provide any reason why effectiveness may be lower in this group, or may a difference simply be associated with sampling and study design?

Company response: Any differences in NMA effectiveness estimates for cemiplimab + chemotherapy vs. pembrolizumab + chemotherapy across histology and PD-L1 expression level subgroups are more likely to be associated with sampling and study design. The PD-L1 ≥ 50%, squamous histology subgroup (n = 65) represents 20% of the EMPOWER-Lung 3 MHRA label population and 14% of the EMPOWER-Lung 3 ITT population. Therefore, any results should be interpreted with caution. That said, the data show a broadly consistent magnitude and direction of treatment effect across histology and PD-L1 subgroups, as shown in Section B.2.7.2 of the original submission.

B8. Priority question: Section B.3.5, page 155: It states "The distribution of chemotherapy regimens was assumed to the same for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy." The distribution of pre-progression treatments is different in the Excel model. Please explain the difference in the submission text and in the Excel model. Please clarify what the distribution of treatments should be for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy in the model, and clarify the source of that information.

Company response: Please note that rows 120-122 in the **Input_Drug_Costs** sheet of the model were inadvertently hidden such that paclitaxel + carboplatin costs for the pembrolizumab + chemotherapy were not visible. We confirm that the distribution of chemotherapy in the model are the same in both the cemiplimab + chemotherapy and pembrolizumab + chemotherapy arms. This can be demonstrated by assuming equal efficacy between the two arms (by applying the cost comparison setting), setting administration costs to zero (as there is an imbalance due to Q6W

pembrolizumab) and applying 100% discounts to both pembrolizumab and cemiplimab to remove the IO costs. It can then be seen that the pre-progression drug acquisition costs in both arms are the same (see the **Results_1** sheet in the model). This confirms that the chemotherapy distribution is identical in both treatment arms of the model.

Furthermore, there is a rounding error in Table 52 of the original submission, which we thank the EAG for bringing to our attention. A corrected version of the table is given below. For all the model arms, the distribution of chemotherapy was based on the pooled EMPOWER-Lung 3 arms. This approach ensures that any drug cost differences in the model are due to cost of the IOs rather than any differences due to heterogeneity in chemotherapy use across the clinical studies. We consider this to be a conservative approach because, as previously discussed, the use of cemiplimab may offer more flexibility of choice of chemotherapy backbone, including reduced need for pemetrexed-based chemotherapy (which does not currently have generic options) for people with non-squamous disease, and lower starting dose (AUC5) for people with squamous disease and treated with carboplatin.

Table 6: Percentage of usage of each chemotherapy regimen for cemiplimab + chemotherapy and pembrolizumab + chemotherapy (updated Table 52 from Document B)

Intervention	Chemotherapy regimens	Proportion of patients receiving each chemotherapy regimen (28)
Cemiplimab + chemotherapy or pembrolizumab + chemotherapy	Pemetrexed + cisplatin	8.80%
	Pemetrexed + carboplatin	34.98%
	Paclitaxel + cisplatin	5.36%
	Paclitaxel + carboplatin	50.86%
	Pemetrexed maintenance	11%

Note: Proportions from pooled cemiplimab + chemotherapy and chemotherapy alone arms from EMPOWER-Lung 3.

Section C: Textual clarification and additional points

C1. There are errors in the tables in the cost-effectiveness results sections (Table 64 onwards) with the incremental costs, incremental life years, incremental QALYs and ICERs being in the incorrect row (indicating that Pembro + Chemo is dominant rather than Cemiplimab + chemo). For completeness please could the company provide corrected tables and check that there are no similar errors in the other tables.

Company response: Our approach is a common approach/format used in appraisals, as in cases where more than one comparator is included in the analysis, this format allows results to be displayed for multiple treatment comparisons against the intervention treatment. Given the single relevant comparator addressed in our submission (i.e., pembrolizumab + chemotherapy), we have updated and attached alongside this response versions of our submission (Documents A and B) with revised table formatting as suggested for clarity.

References

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Appendices

Appendix 1: Data extraction (clinical SLR)

All data of interest were extracted from primary publications, whereas only additional data reported for relevant outcomes of interest or subgroups of interest (listed in Table 1 of the clinical SLR report) were extracted from subsequent publications. Data extraction was conducted by two reviewers working independently. Any discrepancies between reviewers were resolved through discussion, involving a third reviewer if necessary. Data were stored and managed in a Microsoft Excel workbook (see Appendix F of the clinical SLR report)

Trial characteristics

The following trial characteristics were extracted: trial name; trial authors; publication year; trial ID and NCT code; trial location (country/region of patient enrolment); trial objectives; trial design; trial phase; blinding; randomization**;** crossover, including conditions for crossover, crossover treatment details, and proportion of patients who crossover; sample size at baseline; number of patients randomized; number of patients who completed the trial; trial duration, initiation, and completion cut-off dates; trial inclusion and exclusion criteria; treatment arms; trial outcomes, including definitions (primary endpoints; secondary endpoints); pre-planned subgroups; follow-up period; PD-L1 expression testing method, including details of tumor proportion score (TPS), combined positive score (CPS), tumor-infiltrating immune cell (IC) scoring; IHC-specific assays; and whether additional oncogenic biomarkers (EGFR, ALK, ROS-1) were tested.

Treatment characteristics

The following treatment characteristics were extracted: treatment regimen; treatment dose; method of administration; frequency of administration; treatment duration; concomitant/background therapies; palliative treatment (if any).

Baseline patient characteristics

The following baseline patient characteristics were extracted: age; sex; race; ethnicity; weight; body mass index; smoking status (current/former/never/unknown); Eastern Cooperative Oncology Group (ECOG) performance status, World Health

Organization (WHO) performance status, Zubrod Score, Karnofsky performance status; disease stage (metastatic vs. non-metastatic [locally advanced]), including American Joint Committee on Cancer (AJCC) classification; primary tumor location; number and location of metastatic site(s); prior treatment for early-stage disease; type of treatment (e.g., surgery, radiotherapy, adjuvant radiotherapy; systemic therapy as part of the multimodal treatment for early-stage disease); newly diagnosed advanced; progressed from lower stage to advanced stage; histological subtype (non-squamous and/or squamous); molecular testing results (EGFR, ALK, ROS-1), including proportion of patients with mutation status not reported; PD-L1 expression level.

Outcomes

The following efficacy outcomes were extracted: OS, PFS, time to progression (TTP), and ToT (including HRs along with 95% CIs**,** corresponding proportions at the 1-year landmark along with 95% CIs and total number of events [where reported], median [months] and 95% CI, and availability of Kaplan–Meier [KM] curves); measures of response, including objective response rate (ORR; defined as complete response [CR] or partial response [PR], both of which were extracted separately); disease control rate (defined as CR, PR, or stable disease); tumor response criterion (e.g., Response Evaluation Criteria in Solid Tumors [RECIST], modified RECIST, or WHO); time to tumour response (TTR; e.g., initial response if reported, 6 months, best response in the period over which the patient was followed); duration of response (DOR); duration of disease control.

In addition, the following safety outcomes were extracted: AEs (captured as the proportion of patients), including IMAEs (any grade, grade 3-5); all-cause AEs (any grade, grade 3-5); treatment-related AEs (any grade, grade 3-5); serious adverse events (SAEs; all-cause and treatment-related); all-cause mortality; treatment-related deaths; duration over which safety outcomes were reported (mean, standard deviation [SD], median, minimum, maximum); discontinuation due to AEs (DAEs; all-cause and treatment-related); and criteria used to define AEs and their severity (e.g., common terminology criteria for adverse events [CTCAE]).

For dichotomous outcomes, the number of patients with the event and the number of patients in each treatment arm were extracted, along with relative measures and

associated information regarding uncertainty. For continuous outcomes, the value and change from baseline in all intervention groups were extracted along with associated information regarding uncertainty. If the change from baseline was not provided, the score at end of follow-up and the baseline score were extracted. For event rates, the number of events, the number of patients in each treatment arm, and follow-up or exposure time were extracted. For time-to-event outcomes, HRs and associated information regarding uncertainty were extracted. Kaplan-Meier (KM) curves corresponding to the longest follow-up duration from peer-reviewed full-text publications were extracted in terms of the proportion of patients who had an event over time using DigitizeIt® (DigitizeIt; http://www.digitizeit.de/) in addition to the number of patients at risk over time. Where KM curves were not available in peer-reviewed publications for a given trial, the longest follow-up duration from conference materials was selected for digitization.

Means were favored over medians if both were provided. Measures of dispersion were extracted using the following hierarchy: standard error, standard deviation, confidence intervals, p-values, interquartile ranges, and ranges. When multiple measurements were available, the two highest measurement on the hierarchy was extracted.

When information was available for multiple populations, data were extracted using the following hierarchy: the intention to treat (ITT) population, followed by the full analysis set (FAS), modified intention to treat population (mITT), and the per protocol (PP) population. As with dispersion, only the preferred population was extracted. For safety outcomes, the safety analysis set (SAS) was extracted.

Study quality

Two independent reviewers assessed the risk of bias of the included studies for which full-text publications were available. Following reconciliation between the two investigators, a third investigator was included to reach consensus for any remaining discrepancies. The Cochrane Collaboration's Risk of Bias tool was used to assess risk of bias in included clinical trials (see Appendix B in the clinical SLR report) (29). This instrument was used to evaluate six key domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.

The risk of bias instrument can be used to assign summary assessments of within study bias: low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), or high risk of bias (high risk of bias for one or more key domains).

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

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, work in lung cancer patient care (information, support and advocacy activity) and raise awareness of the disease and issues associated with it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	**RCLCF has received the following funding :** - Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project; £15,000 grant for Information Services; £165 Advisory Meeting Honorarium) - BMS (£30,000 for 1 year funding of GLCC project; £1100 for Advisory board Honorarium) - Lilly (£30,000 for 1 year funding of GLCC project) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £1040 Advisory board Honorarium) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations) - Sanofi (£30,000 for1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project)

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	- Astra Zeneca (£30,000 for 1 year funding of GLCC project; £19,500 for GLCC Project Translation; £300 for Advisory Board Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium) - Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker Fee) - Janssen (£24,000 grant funding for Ask The Nurse Service)
4c. 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 carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, Patient Information Days, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	According to the National Lung Cancer Audit, the one year survival for lung cancer at all stages, is 48% (for those diagnosed in England in 2022). Thus, this group of lung cancer patients, with advanced disease have a particularly poor outlook, with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	As above, despite current therapy, outcomes for those with advanced disease remains poor. In recent years, immunotherapy has brought a new therapy option.
8. Is there an unmet need for patients with this condition?	Yes.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We note the results of the EMPOWER Lung-3 study of Cemiplimab plus chemotherapy versus chemotherapy alone. After 28.4 months of follow up, median OS was 21.9 months in the Cemiplimab plus chemotherapy arm and 13.0 months in the chemotherapy plus placebo arm. Median progression free survival was 8.2 months, versus 5.5 months in the chemotherapy alone arm. Results are broadly in line with those seen for Pembrolizumab in the KEYNOTE trials. Although, there is, of course, no head to head comparison data. It is noted that chemotherapy regimens were more flexible than in trials with the standard immunotherapy agent. This flexibility may ensure immunotherapy access for some patients, who would struggle to receive more toxic chemotherapy (for example, older patients and / or those with impaired renal function).

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The side effects associated with Cemiplimab and chemotherapy.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

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

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• In patients with advanced non small cell lung cancer, Cemiplimab plus chemotherapy shows improved overall survival as compared with chemotherapy alone. • Cemiplimab brings a needed treatment alternative to standard of care in the advanced non small cell lung cancer treatment setting.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Professional organisation submission

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.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	British Thoracic Oncology Group/
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	Funded by sponsorship and registration fees for educational learning for HCP's with an interest in thoracic oncology
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes BTOG 2024 annual conference sponsorship £30,000 + VAT
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

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, or prevent progression or disability.)	To improve survival and delay progression in patients with metastatic (incurable) non-small cell lung cancer while maintaining quality of life.
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.)	Improvement in median OS of 3 months over comparator
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Comparatively to other cancer types, NSCLC have relatively poor outcomes and as such treatments in this area are required. There are other similar treatments for this patient population already available to NHS patients.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Options include: 1. Single agent immunotherapy (pembrolizumab or atezolizumab) in PDL1 >50% population 2. Combination chemo-immunotherapy (pembrolizumab and platinum-based chemotherapy) for PDL1 all comers 3. Platinum-doublet chemotherapy (immunotherapy ineligible or frail)

	These are ***without actionable genomic mutations***
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guideline [NG122]
9b. 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 of care. The subjective area is that in PDL1 >50% adenocarcinoma is the combination of platinum-doublet chemotherapy with pembrolizumab should only be offered '**Only if urgent clinical intervention is required'** and therefore single agent pembrolizumab or atezolizumab in this population is preferred option. Experience within NHS England.
9c. What impact would the technology have on the current pathway of care?	It offers an additional option for patients with PDL1 >50% NSCLC. There is a higher proportion of squamous cell lung cancer patients in the cemiplimab phase 3 study (and stage 3 patients). Squamous cell NSCLC is a more challenging patient population to treat with poorer outcomes. This has an over-representation of squamous cell carcinoma in this trial and also has demosntraterd benefit in squamous cell carcinoma of the skin. It may see a switch of treatment from current standard of care to cemiplimab for squamous cell lung cancer.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	No change in resource requirements. Delivered every 3 weeks. Although current standard of care has option for reduced frequency (pembrolizumab 6 weekly)
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology services (secondary / tertiary care)

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Comparitor arm for the clinical studies was platinum-doublet chemotherapy (historical control). Since that time the standard of care has progressed to immunotherapy and as such it is an additional option for patients with NSCLC. There is potential for it providing a clinically meaningful improvement for those NSCLC patients with squamous cell lung cancer given their over-representation in the cemiplimab phase 3 study and its results.
11a. Do you expect the technology to increase length of life more than current care?	Potential in squamous cell population.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Potential in squamous cell population
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective: PDL1 >50% NSCLC Potential for Squamous cell population

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	No difference (substitution of current immunotherapy with different immunotherapy)

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.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional rules
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?	No
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 improve the way that current need is met?	No. Not over current treatments on offer. High proportion of stage 3 cases in the phase 3 clinical trial as such may address a patient population where need is high.

16a. Is the technology a 'step-change' in the management of the condition?	Potentially. Small improvement in responses with the caveat that there is no head to head data for different immunotherapy agents. Potential for improved outcomes observed given the higher representation of squamous population but this is with the caveat there is a higher stage 3 population and this may indeed be the confounding factor.
16b. Does the use of the technology address any particular unmet need of the patient population?	Only if there is significant benefit in the squamous population as this is a difficult to treat sub-population of NSCLC
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?	Significant impact on quality of life. Immunotherapy toxicities are unpredictable and of variable grades / levels. This is important across all immunotherapies and particularly for frail, co-morbid patients with NSCLC.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Control arm is historical (platinum doublet) while current treatment already includes immunotherapy in front line setting
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important	Overall Survival, Progression free survival, toxicity profile and quality of life.

outcomes, and were they measured in the trials?	
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA770]?	Yes - https://www.oncologypipeline.com/apexonco/world-lung-2024-picking-apart-harmoni-2-win Not yet published. Presented at world lung on 10/9/2024. Data immature for OS.
21. How do data on real-world experience compare with the trial data?	Across most studies real world data show inferior outcomes compared to trial data in lung cancer populations. No real world evidence that I am aware of in this appraisal.

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.	

Topic-specific questions

23. Which treatments would be displaced by cemiplimab with platinum chemotherapy if it were recommended for use in the NHS?	Pembrolizumab with platinum-doublet chemotherapy.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Would provide additional treatment for those with PDL1 >50% NSCLC in combination with platinum-doublet chemotherapy • The trials have an over-representation of squamous cell NSCLC and stage III. This confounds the results although identifies a potential for unmet need in the difficult to treat squamous cell population. This result may well be artefact and cross-trial comparison challenging. • The technology would have no change in baseline resource requirements delivered every 3 weeks (although pembrolizumab has option of 6 weekly) • •

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Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Evidence Assessment Group Report

Produced by Newcastle University

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Contributions of authors: Stephen Rice acted as project lead. Louise Tanner acted as lead effectiveness reviewer. Tomos Robinson acted as lead cost effectiveness reviewer. Kate Lanyi and Negar Yousefzadeh acted as assistant effectiveness reviewers. Lakshmi Jayachandran acted as assistant cost effectiveness reviewer. Fiona Beyer and Claire Eastaugh reviewed the literature search methods. Nick Meader assisted with the review of the Network Meta Analysis.

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

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Report key: Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Abbreviations

AEs	Adverse events
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
AUC	Area under the curve
BIC	Bayesian information criterion
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CEACs	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CrI	Credible interval
CS	Company submission
CUA	Cost utility analysis
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
ECOG PS	ECOG Performance Status
EGFR	Epidermal growth factor receptor
eMIT	Drugs and pharmaceutical electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	The EORTC Core Quality of Life Questionnaire
GBP	Pounds sterling
GHS	Global health status
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health-state utility values

HTA	Health technology assessment
IC	Investigator's choice
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
IMAEs	Immune-mediated adverse events
IO/IOs	Immunotherapy/immunotherapies
ITT	Intention-to-treat
IV	Intra-venous
MeSH	Medical Subject Headings
MHRA	The Medicines and Healthcare products Regulatory Agency
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PBAC	The Pharmaceutical Benefits Advisory Committee
PD	Progressed Disease
PD-L1	Programmed death-ligand 1
PF	Progression-free
PfC	Points for clarification

PFS	Progression-free survival
PRESS	Peer Review of Electronic Search Strategies
PSA	Probabilistic sensitivity analysis
PSM	Propensity score matching
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
Q3W	Every three weeks
Q6W	Every six weeks
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RoB	Risk of bias
ROS	Proto-oncogene tyrosine-protein kinase
ROS-1	ROS proto-oncogene 1
SAEs	Severe adverse events
SE	Standard error
SLR	Systematic literature review
SoC	Standard of care
TA	Technology appraisal
TAR	Technology assessment reviews
TEAEs	Treatment emergent adverse events
ToT	Time on treatment
TTD	Time to death
UK	United Kingdom

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1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 presents the model outcomes. Section 1.3 summarises all key issues identified by the EAG relating to clinical effectiveness and cost-effectiveness. Section 1.4 summarises the EAG's preferred assumptions and ICERs.

Further detail regarding key and non-key issues are described in the main EAG Report (Sections 2 to 6).

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of EAG's key issues

Issue number	Brief summary of issue	Report section(s)
1	The population who would be eligible to receive cemiplimab + chemotherapy is a subset of the NICE scope	2.1
2	The comparator included in the company's decision problem does not reflect all of the treatments in the NICE scope and clinical pathways for the population of interest	2.2
3	Uncertainty surrounding the transitivity assumption in the NMA	3.3.3
4	Uncertainty in the assumptions regarding treatment discontinuation	4.2.4
5	Uncertainty in the treatment waning assumptions made in the economic model	4.2.5
Abbreviations: EAG = Evidence Assessment Group; NMA = network meta-analysis		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained. A technology is considered absolutely dominant when it improves quality of life (measured in QALYs gained) and reduces costs (measured in £GBP) relative to its best alternative treatment.

Overall, in the company economic model (CEM) the technology is modelled to affect QALYs by:

- Increasing overall survival (OS)

- Decreasing pre-progression survival time
- Increasing post-progression survival time
- Reducing the number of grade 3+ adverse events (AEs)

Overall, in the CEM the technology is modelled to affect costs by:

- Modelling greater Time on Treatment (ToT) for cemiplimab than for pembrolizumab (in scenario 4 in the CS and in the EAG base case) increases drug acquisition costs
- Increasing total disease management costs (made up of pre-progression, progressive disease and terminal care)
- Reducing the number of grade 3+ AEs

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

- Choice of parametric survival model for OS: In the company base-case, the company use a log-logistic distribution for the OS chemotherapy reference curve. Using alternative distributions, such as gamma and generalized gamma, decreases the incremental QALY gain for cemiplimab + chemotherapy.
- Treatment discontinuation: In the company base-case, the company assume that ToT is equal to progression free survival (PFS). Estimating ToT through application of a PFS versus ToT hazard ratio (HR) decreases the treatment costs for pembrolizumab + chemotherapy.
- Treatment waning assumption: In the company base-case, the company assumed that there was a continuation of the treatment effect from 24 months to 60 months, after which there an “immediate” waning, in which the estimated hazard of death is assumed to be equal to chemotherapy at five years for both PFS and OS. Using a “gradual” waning decreases the incremental QALY gain for cemiplimab + chemotherapy.
- Utilities for the progression-free (PF) and progressed-disease (PD) health states: In the company base-case, the company use estimates from the EMPOWER-Lung 3 trial[1], mapped to the EQ-5D-3L from the EORTC-QLQ C30. Using alternative utility values previously used in NICE submissions in this clinical area decrease the incremental QALY gain for cemiplimab + chemotherapy.

1.3 Description of the EAG's key clinical and economic issues

Table 1.2: Key issue 1: The population who would be eligible to receive cemiplimab + chemotherapy is a subset of the NICE scope.

Report section	Section 2.1
Description of issue and why the EAG has identified it as important	The company's decision problem is aligned with the population in the NICE scope. However, the sub-groups within this population who would be eligible to receive cemiplimab + chemotherapy are: • Patients with NSCLC, PD-L1 1-100%, no targetable mutations, non-squamous sub-group who are not contraindicated to receive IO + chemotherapy • Patients with NSCLC, PD-L1 1-49%, no targetable mutations, squamous sub-group who are not contraindicated to receive IO + chemotherapy • Patients with NSCLC, PD-L1 ≥50%, no targetable mutations, squamous sub-group where urgent clinical intervention is needed Patients with PD-L1 ≥50% in the squamous sub-group who do not require urgent clinical intervention, as well as patients from other subgroups who are contraindicated to IO + chemotherapy would therefore be ineligible for cemiplimab + chemotherapy.
What alternative approach has the EAG suggested?	None. The EAG note that the company provided evidence for the effectiveness of cemiplimab + chemotherapy in patients who would otherwise have received pembrolizumab + chemotherapy.
What is the expected effect on the cost effectiveness estimates?	There is only cost effectiveness evidence for patients who would otherwise have received pembrolizumab + chemotherapy.
What additional evidence or analyses might help to resolve this key issue?	None

Report section	Section 2.1
Abbreviations: NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; EAG = evidence assessment group; IO = immunotherapy	

Table 1.3: Key issue 2: The comparator included in the company's decision problem does not reflect all of the treatments in the NICE scope and clinical pathways for the population of interest

Report section	Section 2.2
Description of issue and why the EAG has identified it as important	The company only included one comparator (pembrolizumab + chemotherapy) in their decision problem, despite various other treatment options being available in the NICE scope and clinical pathways for the population of interest.
What alternative approach has the EAG suggested?	The clinical advisor to the EAG confirmed that pembrolizumab + chemotherapy is the only suitable comparator for cemiplimab + chemotherapy, as both treatments would only be offered to patients who are not contraindicated to IO + chemotherapy and to patients with PD-L1 ≥50%, squamous histology who require urgent clinical intervention. As such, the EAG does not suggest an alternative approach in terms of the comparators against which cemiplimab + chemotherapy should be compared.
What is the expected effect on the cost effectiveness estimates?	There is only evidence for the cost-effectiveness of cemiplimab + chemotherapy compared to pembrolizumab + chemotherapy.
What additional evidence or analyses might help to resolve this key issue?	None.
Abbreviations: NICE = National Institute for Health and Care Excellence; PD-L1 = programmed death-ligand 1; EAG = Evidence Assessment Group; IO = immunotherapy	

Table 1.4: Key issue 3: Uncertainty surrounding the transitivity assumption in the NMA

Report section	Section 3.3.3
Description of issue and why the EAG has identified it as important	The company reported that the difference in effect modifier trial characteristics across trials in the NMA was not known and the potential for bias related to this could not be assessed. In particular, the percentage of patients receiving subsequent immunotherapy in the chemotherapy control arm

Report section	Section 3.3.3
	of the KEYNOTE studies investigating pembrolizumab combination therapy was not reported at the key time point.
What alternative approach has the EAG suggested?	There is no alternative approach that can be taken in this submission.
What is the expected effect on the cost effectiveness estimates?	The effect is unknown. While the percentage of patients receiving cross-over treatment at the relevant timepoint was not reported in the KEYNOTE studies, roughly 41-42% had pembrolizumab crossover treatment following chemotherapy at 5 years in KEYNOTE-189 and KEYNOTE-407. If the percentage receiving subsequent immunotherapy treatment were higher in the chemotherapy control arms of the pembrolizumab trials than in the cemiplimab EMPOWER trial, this would likely favour cemiplimab for the OS outcome. Were that the case, the incremental QALYs for cemiplimab would be lower and cemiplimab would likely be less cost-effective than in the base case. The potential for bias associated with other effect modifiers is unknown.
What additional evidence or analyses might help to resolve this key issue?	The authors of the studies included in the NMA could be contacted to see if the relevant information exists (i.e. baseline characteristics between groups for patients with PD-L1 ≥1) and whether they could provide the information. Individual patient data across included studies in the NMA would be required to try to adjust for any subsequent treatment discrepancies.
Abbreviations: EAG = Evidence Assessment Group; NMA = network meta-analysis	

Table 1.5: Key issue 4: Uncertainty in the assumptions regarding treatment discontinuation

Report section	Section 4.2.4
Description of issue and why the EAG has identified it as important	In the base case analysis, the company assumed that the Time on Treatment (ToT) was equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy, guided by an advisory board meeting where advisors were cautious about concluding discrepancies between cemiplimab + chemotherapy and pembrolizumab + chemotherapy treatment arms. The EAG notes that assuming that ToT is equal to PFS will underestimate the costs for cemiplimab + chemotherapy and overestimate the costs for pembrolizumab + chemotherapy.
What alternative approach has the EAG suggested?	For consistency with the effectiveness estimates, either the ToT estimates should be estimated from the respective clinical trials (EMPOWER-Lung 3[1] and KEYNOTE-407) as

Report section	Section 4.2.4
	well as effectiveness, or instead both effectiveness and ToT should be assumed to be equal. In the EAG base case, the former approach is taken: the hazard rates of ToT from EMPOWER-Lung 3[1] and KEYNOTE-407 are used to estimate time on treatment.
What is the expected effect on the cost effectiveness estimates?	In Scenario 4 of the company's scenario analyses, the company used the hazard rates (taken from EMPOWER-Lung 3[1] and KEYNOTE-407) to PFS to estimate time on treatment. The incremental costs changed from [redacted] in in the company base case to [redacted], decreasing the cost-effectiveness of cemiplimab + chemotherapy.
What additional evidence or analyses might help to resolve this key issue?	Further evidence that ToT beyond PFS does not affect OS in the relevant population treated with cemiplimab + chemotherapy would reduce the level of uncertainty regarding this issue.
Abbreviations: EAG = Evidence Assessment Group; QALY = quality-adjusted life year; ToT = Time on Treatment; PFS = progression-free survival; OS = overall; survival	

Table 1.6: Key issue 5: Uncertainty in the assumptions regarding treatment waning

Report section	Section 4.2.5
Description of issue and why the EAG has identified it as important	In the CEM, the company assumed that there was an "immediate" waning of the treatment effect for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. The EAG is concerned that applying waning on this "immediate" basis does not reflect the mechanism of action of IOs and lacks face validity.
What alternative approach has the EAG suggested?	As part of the EAG base case, the EAG has included a "gradual" waning of the treatment effect for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy beginning at 24 months (in line with the stopping rule for both treatments) and ending at 5 years.
What is the expected effect on the cost effectiveness estimates?	Assuming a "gradual" waning of the treatment effect rather than an "immediate" waning reduces the incremental QALYs for cemiplimab + chemotherapy from [redacted] in the company base case to [redacted], thus decreasing the cost-effectiveness of cemiplimab + chemotherapy.
What additional evidence or analyses might help to resolve this key issue?	Further evidence on the level of attenuation of treatment effects over time for cemiplimab would help to resolve this uncertainty.
Abbreviations: EAG = Evidence Assessment Group; QALY = quality-adjusted life year; CEM = cost-effectiveness model; IOs = immunotherapies	

1.4 Summary of the EAG's preferred assumptions and ICER

Three changes were made from the company's base-case to the EAG base-case.

In the company base-case, the company assume that the ToT was equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. In the EAG base-case, the HRs of ToT estimated from EMPOWER-Lung 3[1] for cemiplimab + chemotherapy and KEYNOTE-407 and KEYNOTE-189 for pembrolizumab are used. This aligns with Scenario 4 from the CS.

In the company base case, the company assumed that there was a continuation of the treatment effect from 24 months to 60 months, after which the estimated hazard of both disease progression and death is assumed to be equal to chemotherapy at five years for both PFS and OS. In the EAG base, a gradual linear waning effect for both PFS and OS starting at 24 months (in line with the stopping rule for both cemiplimab and pembrolizumab) and ending at 60 months is used, after which the hazard of cemiplimab + chemotherapy and pembrolizumab + chemotherapy is assumed to be equal to the hazard for chemotherapy.

In the company base case, treatment-specific AE profiles are used, despite the chemotherapy backbone regime being assumed to be the same across treatments. In the EAG base, the AE profile for pembrolizumab + chemotherapy has been applied to both treatment arms.

The probabilistic results from the company and EAG base-case are shown in

Table 1.7. Selected results from the company and EAG's deterministic scenario analysis are shown in

Table 1.8.

Table 1.7 Probabilistic results from company and EAG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Probabilistic					
Cemiplimab + chemo	[redacted]	[redacted]	-	-	-
Pembrolizumab + chemo	£126,224	2.16	[redacted]	[redacted]	Dominating
EAG base-case – Probabilistic					
Cemiplimab + chemo	[redacted]	[redacted]			
Pembrolizumab + chemo	£116,595	2.11	[redacted]	[redacted]	Dominating
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year					

Table 1.8: Selected results from company and EAG's deterministic scenario analysis

Scenario	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	EAG base-case	**N/A**	[redacted]	[redacted]	Dominating
CS 2	OS reference and two-step NMA (log-logistic)	Alternative OS reference and two-step NMA (generalised gamma)	[redacted]	[redacted]	Dominating
CS 3	PFS 2-step NMA (log-logistic)	PFS constant HR NMA (log-logistic), no violation of PH assumption for PFS	[redacted]	[redacted]	Dominating
CS 5	Waning of treatment effect applied to PFS/OS from 24 to 60 months	Waning of treatment effect applied to PFS/OS from 36 months	[redacted]	[redacted]	Dominating
CS 8	Health state utility values (EMPOWER-Lung 3 trial, EORTC to EQ-5D-5L mapping (UK tariff, modelled average)	Alternative health state utility values (NICE TA584 atezo+bev+chemo non-squamous IMpower 150 utilities using UK tariff)	[redacted]	[redacted]	Dominating
CS 10	Discount applied to pembrolizumab list price is 0%	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-utility analysis	[redacted]	[redacted]	[redacted]
CS 11	Discount applied to pembrolizumab list price is 0% in cost-utility analysis	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-comparison analysis	[redacted]	[redacted]	Increased cost in cost-comparison analysis

CS 17	AE costs in the pembrolizumab + chemotherapy arm assumed equal to the EMPOWER-Lung 3 data in the cost-comparison analysis	Include AE costs from KEYNOTE 189 and KEYNOTE 407 in the pembrolizumab + chemotherapy arm of the cost-comparison analysis (instead of assuming equal to EMPOWER-Lung 3)	[redacted]	[redacted]	Cost saving in cost-comparison analysis
EAG 9	OS reference and 2-step NMA (log-logistic)	OS reference and 2-step NMA (gamma)	[redacted]	[redacted]	Dominating
EAG 10	PFS and OS reference and 2-step NMA (log-logistic)	Generalized gamma distribution for PFS + gamma distribution for OS	[redacted]	[redacted]	Dominating
EAG 11	PFS/OS utilities from EMPOWER-Lung 3 trial, mapped from EORTC to EQ-5D-5L	Alternative utility values for PFS/OS from Nafees et al 2008)	[redacted]	[redacted]	Dominating

Abbreviations: CS = Company Submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality-adjusted life year

2 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the EAG's critique of the company's decision problem is presented in Table 2.1 below. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key issue, some concerns or appropriate).

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with untreated locally advanced (which is not a candidate for definitive chemoradiation) or metastatic NSCLC, which expresses PD-L1 on 1% or more of tumour cells and has no EGFR, ALK or ROS-1 genetic alterations	As per scope	N/A	**Key issue 1** Cemiplimab + chemotherapy would not be suitable for the whole population defined in the NICE scope. See section 2.1 for further details.
Intervention	Cemiplimab with platinum-based chemotherapy	As per scope	N/A	**Appropriate** As per the NICE scope
Comparator(s)	For people with squamous NSCLC whose tumours express PD-L1 on 1 to 49% of tumour cells:	For people with squamous and non-squamous NSCLC whose tumours express	Regeneron considers pembrolizumab + chemotherapy (which has >80% market share among NICE-recommended immunotherapy (IO) + chemotherapy	**Key issue 2** The company included only one comparator from the NICE scope, namely pembrolizumab + chemotherapy, in their decision

	• Platinum doublet chemotherapy • Pembrolizumab with carboplatin and paclitaxel For people with squamous NSCLC whose tumours express PD-L1 on 50% or more of cells: • Platinum doublet chemotherapy • Pembrolizumab monotherapy • Atezolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel (for people in need of urgent clinical intervention) For people with non-squamous NSCLC whose tumours express PD-L1 on 1 to 49% of tumour cells: • Pembrolizumab with pemetrexed and platinum chemotherapy • Atezolizumab with bevacizumab,	PD-L1 on greater than 1% of tumour cells: Pembrolizumab + chemotherapy per NHS England commissioning policies[2]	options across histologies and PD-L1 expression levels ≥1%)[3] to be the only relevant comparator for this appraisal: Feedback from UK clinical expert lung oncologists consulted during development of this submission confirmed that patients offered IO + chemotherapy comprise a patient group who are clinically distinct from those who would typically be offered chemotherapy alone because they are not considered suitable for IO, or from those who would typically be offered an IO monotherapy instead of in combination with chemotherapy. The only other NICE-recommended IO given in combination with chemotherapy is atezolizumab (TA584), which is available for use only in people with non-squamous disease and PD-L1 1-49%, and is not commonly used in UK clinical practice (having approximately 8% of market share in that population)[3] UK clinical expert lung oncologists have confirmed that pembrolizumab	problem, despite various other treatment options being available (CS Table 1, Section B.1.1, pp.12-13).[4] See section 2.2 for further details.

	carboplatin and paclitaxel • Pemetrexed with platinum doublet chemotherapy For people with non-squamous NSCLC whose tumours express PD-L1 on 50% or more of cells: • Pembrolizumab with pemetrexed and platinum chemotherapy • Pembrolizumab monotherapy • Atezolizumab monotherapy • Pemetrexed with platinum doublet chemotherapy		+ chemotherapy is the relevant comparator that would be displaced by use of cemiplimab + chemotherapy Overall, cemiplimab + chemotherapy will primarily act as an alternative to the current standard of care for the first-line treatment of patients in the PD-L1 ≥1%, any histology population for which it is licensed (i.e., pembrolizumab + chemotherapy)	
Outcomes	Progression-free survival (PFS) Response rates Overall survival (OS) Adverse effects of treatment Health-related quality of life	As per scope	N/A	**Appropriate** There original primary outcome reported in the protocol[1] for EMPOWER-Lung 3 trial was PFS, as opposed to OS. This was justified by the company as OS could be confounded by subsequent treatments people received whose cancer progressed. However, OS was the primary outcome that was

				reported in the EMPOWER-Lung 3 trial (CS Table 5, Section B.2.3.1, p.37).[4] The company reported results for both outcomes, therefore the EAG does not consider this to be a key issue.
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. 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.	A cost-comparison analysis (assuming equivalent clinical outcomes) is included as an alternative base case alongside a cost-utility analysis.	A key challenge associated with conducting a cost-utility analysis to address the relevant decision problem on the cost-effectiveness of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy is the lack of head-to-head RCT evidence. As expected, there were limitations in conducting the NMA (due to inherent limitations in the evidence base and a lack of published data for the relevant comparator), and the results are associated with uncertainty as reflected in wide credible intervals. However, all the available evidence from the trial data, previously published NMA, and the Company NMA points to a conclusion of similar efficacy. This view is shared by UK clinical experts	**Some concerns** The EAG has several concerns regarding the economic analysis, including key issues relating to treatment discontinuation and treating waning assumptions. See Section 4 for further details.

	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		experienced in the use of IO therapy in NSCLC, and by CADTH and PBAC. On this basis, a cost-utility analysis has been provided per the NICE scope and reference case, but a cost comparison analysis has also been provided to facilitate pragmatic decision-making. This pragmatic cost comparison approach was accepted previously by NICE (e.g. in TA705) and by both CADTH and PBAC. As described in more detail in Section B.3, Regeneron believes that currently, the justification for modelling equivalent efficacy for cemiplimab + chemotherapy and pembrolizumab + chemotherapy is stronger than the justification for modelling any differences in efficacy: • Cemiplimab and pembrolizumab have the same mechanism of action • There is no published evidence suggesting differences in OS or PFS between cemiplimab and pembrolizumab	

			• Only cemiplimab + chemotherapy and pembrolizumab + chemotherapy have and NCCN 'preferred' recommendation in advanced/metastatic NSCLC • UK clinical expert lung oncologists noted similarity in efficacy between the two treatments As stated above, a pragmatic cost-comparison approach has previously been accepted by other international HTA bodies.	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Histology • PD-L1 status • Disease stage • Newly diagnosed or recurrent after surgery metastatic disease	Four subgroups will be considered, based on histology and PD-L1 levels, to reflect the current UK treatment pathway: Squamous, PD-L1 1-49% Squamous, PD-L1 ≥50%	The submission will not include subgroup analyses by disease stage or by newly diagnosed or recurrent after surgery metastatic disease for the following reasons: Disease stage In the UK, the Blueteq protocol (i.e. NHS England commissioning policy) permits treatment of patients with locally advanced NSCLC who are not candidates for definitive chemoradiation with pembrolizumab, despite pembrolizumab not having a marketing authorisation in locally	**Some concerns** The company did not undertake sub-group analyses by disease stage. See section 2.3 for further details.

		Non-squamous, PD-L1 1-49% Non-squamous, PD-L1 ≥50%	advanced disease.[2] These patients are therefore managed in the same way as those with metastatic disease, so subgroup analysis by disease stage lacks relevance to UK clinical practice and treatment decisions. Feedback from UK clinical expert lung oncologists suggested that neither clinical outcomes nor costs would be expected to be meaningfully different for patients with locally advanced disease (not eligible for definitive chemoradiation) versus metastatic disease. Although subgroup analysis by disease stage was planned in the overall population of the EMPOWER-Lung 3 RCT, the small number of patients in the study who were in the licensed population (i.e. PD-L1 ≥1%) with locally advanced NSCLC precludes robust subgroup analysis. Newly diagnosed or recurrent after surgery metastatic disease	

			Feedback from UK clinical expert lung oncologists suggested that neither clinical outcomes nor costs would be expected to be meaningfully different for people who have versus those who have not undergone prior surgery for NSCLC.	

Source: CS Section B.1.1, Table 1, pages 10-14.[4] PfCs response[5]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PfC = points for clarification; QALY = quality-adjusted life year; NSCLS = non-small cell lung cancer; PD-L1 = Programmed death-ligand 1; IO = immunotherapy; OS= overall survival; PFS= progression free survival; NMA = network meta-analysis; RCT = randomised controlled trial; IV = intravenous; EGFR = epidermal growth factor receptor; ALK = Anaplastic lymphoma kinase; ROS = Proto-oncogene tyrosine-protein kinase; TA = technology appraisal; Standard of Care (SoC); CADTH = Canadian Agency for Drugs and Technologies in Health; PBAC = The Pharmaceutical Benefits Advisory Committee; UK = United Kingdom; HTA = health technology assessment; NCCN = National Comprehensive Cancer Network

2.1 Population

In their decision problem, the company aligned the population of interest with the NICE scope, namely: *adults with untreated locally advanced (which is not a candidate for definitive chemoradiation) or metastatic NSCLC, which expresses PD-L1 on 1% or more of tumour cells and has no EGFR, ALK or ROS-1 genetic alterations*. However, the company focused on one comparator from the NICE scope, namely pembrolizumab + chemotherapy, despite multiple alternative treatments being available. This was justified by the company as being due to clinical differences between patients who are eligible to receive IO + chemotherapy versus IO or chemotherapy alone (CS Table 1, Section B.1.1, p.10).[4] The EAG asked the company to clarify which clinical characteristics make people unsuitable for IO + chemotherapy as this represents a subset of patients within the NICE scope who would be ineligible to receive cemiplimab + chemotherapy (PfC A4).[5] The company responded that reasons why some patients are not selected to receive IO + chemotherapy include increased age, comorbidity burden and patient preference (i.e., avoiding side-effects) (PfC A4).[5] The clinical advisor to the EAG agreed with this. The EAG's clinical advisor also explained that for patients in the PD-L1 ≥50%, squamous sub-group, IO monotherapy would be offered as the first line treatment, with chemotherapy being a second line treatment unless urgent clinical intervention is needed; for example, in the case of a rapidly progressing cancer an IO + chemotherapy would be offered as the first line treatment. Based on this, the EAG concludes that cemiplimab + chemotherapy is suitable for patients who would otherwise have been offered pembrolizumab + chemotherapy and the following population sub-groups would not be eligible to receive cemiplimab + chemotherapy:

- Patients who are contraindicated to IO + chemotherapy
- Patients with PD-L1 ≥50% in the squamous sub-group who do not require urgent clinical intervention

2.2 Comparators

The company's decision to focus on one comparator (pembrolizumab +chemotherapy) does not reflect the first line treatments from the NICE scope or clinical pathways for the population of interest, which include a more comprehensive range of treatment options. Data comparing clinical effectiveness, quality of life and adverse events between all comparators in the NICE clinical pathways would enable the EAG to better understand the benefits and harms associated with different treatments. The EAG asked the company to clarify why alternative comparators were excluded from their analyses (PfC A4).[5] The company responded that cemiplimab + chemotherapy represents an alternative treatment option that is suitable for people who would otherwise have received pembrolizumab + chemotherapy (PFC A4).[5] The clinical advisor to the EAG agreed that pembrolizumab + chemotherapy is the relevant comparator for cemiplimab + chemotherapy. The EAG concludes that pembrolizumab + chemotherapy is the recommended current practice in the NHS for the population targeted for cemiplimab + chemotherapy in this evidence submission. While a full incremental cost-effectiveness analysis might include another comparator, pembrolizumab + chemotherapy is the most important comparator in the context.

2.3 Subgroups to be considered

The population in the NICE scope are people with stages IIIB/C and IV disease; however, participants in the EMPOWER-Lung 3 trial were predominantly people with stage IV disease (n=397 in the ITT population (PD-L1 any level); n=280 in the MHRA label population (PD-L1≥1%)) compared to people with stage IIIB/C disease (n=69 in the ITT population (PD-L1 any level); n= 47 in the MHRA label population (PD-L1≥1%)), equating to approximately 85% of people within the sample with stage IV disease (CS Table 6, Section B.2.3.2, p.41).[4] The company did not undertake sub-group analysis by disease stage in the EMPOWER-Lung 3 trial in their submission. The company stated that clinical experts advised that the effectiveness of cemiplimab + chemotherapy is unlikely to vary in relation to disease stage, therefore sub-group analysis by disease stage was not required. The company also noted that the sample size of patients in the PD-L1 population with stage IIIB/C disease was too small for robust analyses by disease stage to be undertaken (CS Table 1, Section B.1.1, pp.13-14).[4] The clinical advisor to the EAG was unable to comment on differences in clinical effectiveness between people with stages IIIB/C and IV disease. However, it was noted that a sample comprising a greater number of people with stage IIIB/C disease may result in increased treatment costs due to the longer survival on average of this population sub-group compared to people with stage IV disease. Regarding the justification for not undertaking sub-group analyses by disease stage, however, the clinical advisor to the EAG agreed that the small sample size for the stage IIIB/C participants would undermine the meaningfulness of results of sub-group analyses by disease stage. Furthermore, sub-group analysis by disease stage was not planned in the protocol for the EMPOWER-Lung 3 trial.[1]

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS describes a systematic literature review (SLR) conducted to identify evidence on the effectiveness and safety of cemiplimab + chemotherapy for treatment of NSCLC. A summary of the EAG's critique is presented in Table 3.1 below. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key issue, some concerns or appropriate).

Table 3.1: Summary of the EAG's critique of the clinical effectiveness systematic literature review

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Data sources	Appendix D, Section D1.1, p.33	**Appropriate** The EAG is satisfied that the company used an appropriate range of data sources.
Search strategies	Appendix D, Section D1.1, p.33-49	**Appropriate** The EAG is satisfied that the search strategies were well reported and appropriate.
Search filters	Appendix D, Section D1.1, pp.33-49	**Appropriate** Search filters were not accurately translated in all cases and some thesaurus headings were exploded in the company search strategy. However, the EAG considers this is unlikely to have led to missing studies.
Eligibility criteria	Appendix D, Section D1.1, Table 70, pp 50-52	**Some concerns** The company included the PD-L1 ≥50%, squamous population sub-group, despite IO monotherapy being the standard of care for these patients according to the NICE clinical pathways for NSCLC. Only studies published in English were included in the SLR, thereby excluding studies published in other languages. The company only included phase 2/3 trials in the systematic literature review and meta-analysis. See Section 3.1.2 for further details.

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Screening	Appendix D, Section D 1.1, Table 70, p. 50-52	**Some concerns** The company did not indicate that they attempted to contact the authors of studies lacking enough information for data extraction and inclusion in the NMA. See section 3.1.3 for details.
Data extraction	Appendix D, Section D 1.1, p. 52	**Appropriate** Data extraction was conducted by two independent reviewers. Any discrepancies that arose were resolved through discussion, with a third reviewer involved if necessary. This independent approach to data extraction significantly reduces the likelihood of errors, enhancing the reliability of the findings.[7]
Quality appraisal	Appendix D, Section D 1.1, Table 77, p. 86	**Appropriate** The company provided the RoB assessment for the nine trials included in the feasibility evaluation for the NMA. All trials were determined to have a low risk of bias according to the Cochrane Collaboration's tool, except for performance bias. Six of the trials were rated as having a high risk of performance bias due to lack of blinding. Following a thorough review, the EAG found the RoB assessment to be appropriate.

Source: Appendix D, Section D1.1, pp.33-68.[8]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence; NMA = Network Meta-Analysis; PfC = points for clarification; PD-L1 = Programmed Death-Ligand 1; IO = Immuno-Oncology; RoB = Risk of Bias; IL – First line

3.1.1 Search methods for the clinical effectiveness SLR

The company conducted separate searches for clinical effectiveness studies.[8] The EAG used the PRESS checklist to appraise the search strategies.[9]

3.1.2 Eligibility criteria

3.1.2.1 Population

- As explained in section 2.1, IO + chemotherapy is suitable for the PD-L1 ≥50%, squamous population sub-group when urgent clinical intervention is needed (i.e., when the disease

is progressing quickly). Hence, the EAG is satisfied that the inclusion of patients with PD-L1 ≥50%, squamous histology in the eligibility criteria for the SLR, was appropriate.

- The company included patients with and without brain metastases in the inclusion criteria for the systematic literature review and NMA, which is a good way to cover diverse cases. However, it would have been helpful if the company had stated whether patients with stable brain metastases (e.g. after treatment) or untreated brain metastases were eligible for inclusion. This could influence the results of the NMA significantly as untreated brain metastases are generally more challenging to manage.
- Patients with "newly diagnosed advanced" and "progressed from lower stage to advanced stage" disease are included in the eligibility criteria for the systematic literature review. It would be useful to know the time since progression, but this information was not reported in the CS. Patients who have recently progressed from a lower stage may have different treatment responses compared to those who have been in an advanced stage for longer periods.

3.1.2.2 Language

Eligible studies in the company's SLR were those published in English (CS Appendix D, Table 70, p.50 to p.52).[10] As it has been suggested that studies conducted in non-English speaking countries are more likely to be published in English journals if they have statistically significant results than studies with statistically non-significant results,[11] it is possible that potentially eligible studies may have been excluded from the SLR, particularly for studies involving IOs other than cemiplimab, which the company may not be aware of.

3.1.2.3 Study designs

In CS appendix D, table 70, the company stated that phase I and IV trials, observational studies were excluded.[10] Since focusing on phase 2/3 trials may enhance comparability across trials of different drugs, the exclusion of other study types (e.g., phase I and IV trials; observational studies) was deemed appropriate, although it may restrict the evidence base and potentially overlook valuable safety and efficacy data, particularly in the case of pembrolizumab for which there are likely to be more studies. Although case reports and case series are often considered lower-quality evidence, they can highlight unique cases or rare side effects that may not be captured in larger studies.

3.1.3 Screening

The company states: "Following the screening, 93 studies were included; of these 43 were ongoing without published results and were subsequently excluded" (CS Appendix D.1, p.52).[10] The company did not report whether they attempted to contact the authors of studies lacking enough information, which might have facilitated the inclusion of pertinent data in the SLR/NMA and potentially affected the results.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

A summary of the EAG's critique of the design, conduct and analysis of the EMPOWER-lung 3 trial is presented in Table 3.2.

Table 3.2: Summary of EAG's critique on the design, conduct and analysis of the EMPOWER-Lung 3 trial

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Intervention	B.2.3.1, Table 5, p.36	**Appropriate** Participants received 350mg (IV) of cemiplimab Q3W with four cycles of chemotherapy. Investigators could choose from one of the following chemotherapy options: • Paclitaxel 200mg/m2 IV plus carboplatin AUC of 5 or 6 mg/ml/min IV on Day 1 of every 21 days for 4 cycles • Paclitaxel 200mg/m2 IV plus cisplatin 75mg/m^2 IV on day 1 of every 21 days for 4 cycles • Pemetrexed 500 mg/m2 IV plus carboplatin AUC of 5 or 6 mg/ml/min IV on day 1 of every 21 days for 4 cycles • Pemetrexed 500mg/m2 IV plus cisplatin 75 mg/m2 IV on day 1 of every 21 days for 4 cycles. The EAG is satisfied that the cemiplimab + chemotherapy intervention in the trial is line with the NICE decision problem.
Comparator	B.2.3.1, Table 5, p.36	**Some concerns** Participants received placebo with four cycles of chemotherapy. Investigators could choose from one of the following chemotherapy options: • Paclitaxel 200mg/m2 IV plus carboplatin AUC of 5 or 6 mg/ml/min IV on Day 1 of every 21 days for 4 cycles • Paclitaxel 200mg/m2 IV plus cisplatin 75mg/m^2 IV on day 1 of every 21 days for 4 cycles • Pemetrexed 500 mg/m2 IV plus carboplatin AUC of 5 or 6 mg/ml/min IV on day 1 of every 21 days for 4 cycles • Pemetrexed 500mg/m2 IV plus cisplatin 75 mg/m2 IV on day 1 of every 21 days for 4 cycles. The EAG has some concerns that the flexibility of investigators choice chemotherapy regimens used in the trial is not reflective of chemotherapy regimens routinely used in UK clinical practice.

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
		See section 3.2.1 for further details.
Randomisation	B.2.3.1, p.34 Appendix D1.3, Table 86, p.91	**Appropriate** Randomisation was performed 2:1 in favour of cemiplimab with chemotherapy versus placebo with chemotherapy via an interactive web response system. The randomisation was stratified by histology (squamous, non-squamous) and PD-L1 expression (<1%, 1-49%, or ≥50%). The EAG is satisfied that the randomisation methods used were appropriate.
Allocation concealment	Appendix D.1.3, Table 86, p.91	**Some concerns** The CS's critical appraisal of allocation concealment for the company's trial was ambiguous. The justification focused on blinding rather than allocation concealment: "Cemiplimab and chemotherapy were prepared for infusion by a pharmacist at the study site. The pharmacist provided site staff with a ready-to-use cemiplimab or placebo infusion solutions that looked identical, allowing the intervention or comparator to be administered in a blinded fashion."
Eligibility criteria	B.2.1, Table 5, p.35	**Appropriate** The inclusion criteria for the trial were: • Patients aged 18 years or older (20 years or older for Japanese participants); • Histologically or cytologically confirmed squamous or non-squamous NSCLC; • ECOG PS ≤1; • Any PD-L1 expression status, • Stage IIIB/C or stage IV NSCLC. • Active or untreated brain metastases were ineligible unless patients were adequately treated, and brain metastases were considered clinically stable • Patients with prior anti-PD-1/PD-L1 therapy and patients whose tumours were positive for EGFR, ALK, or ROS1 mutations were ineligible.

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
		The EMPOWER-Lung 3 trial enrolled patients with any PD-L1 expression status prior to the MHRA licensing cemiplimab with chemotherapy for use in patients with PD-L1 ≥1%. The company presented efficacy and safety data for patients in the MHRA label population (PD-L1 ≥1%) separately to the results presented for the ITT group (PD-L1 any level). The EAG is satisfied that the eligibility criteria of the trial, for patients in the MHRA label population, reflects the patient population in the NICE decision problem who would be eligible to receive IO + chemotherapy.
Blinding	Appendix D.1.1, Table 86, p.91	**Appropriate** Cemiplimab and chemotherapy were prepared for infusion by an unblinded pharmacist at the study site and provided site staff with a ready-to-use cemiplimab or placebo infusion solutions that looked identical so the treatments were administered in a blinded fashion. A blinded independent review committee assessed de-identified radiographs to determine tumour response. An independent data monitoring committee reviewed safety data that were blinded by treatment arm. The EAG is satisfied that the blinding methods used were considered appropriate to avoid introducing bias into the trial.
Baseline characteristics	B.2.3.2, Table 6, p.40 -41 B.2.7, p.58 Appendix E, Table 91, p.99	**Some concerns** The company report that disease characteristics were well balanced between treatment groups at baseline, including for prognostic factors. However, within the MHRA label population, the EAG notes that there are some differences in baseline characteristics between trial arms including age (% people aged ≥65 years; ~7% difference between groups) and sex (% of females;~5% difference between groups), which could act as treatment modifiers. There is also concern the trial population may not be representative of the UK patient population. See section 3.2.2 for further details.

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Dropout rate	Appendix D.1.2, Figure 37, p.90	**Appropriate** The primary reason for treatment discontinuation was disease progression. Of the 312 participants randomised to cemiplimab + chemotherapy group, 240 discontinued treatment, 185 (77%) due to disease progression or death. Of those randomised, the drop-out rate for reasons other than disease progression or death was 23%. Of the 154 randomised to placebo + chemotherapy, 149 discontinued treatment with 110 (74%) due to disease progression or death. Of those randomised, the drop-out rate for other reasons was 26.1%. Other reasons for discontinuation were physician decision, adverse events, withdrawal of consent, patient decision, non-compliance, lost to follow-up and 'other'. The number of drop-outs due to disease progression or death, and other reasons was well balanced between the treatment groups. groups. The EAG does not consider the drop-out rate in the EMPOWER-lung 3 study is likely to introduce bias.
Statistical analyses	B.2.12.1, p.83	**Some concerns** The study was powered to the ITT population (any PD-L1 expression) rather than to the MHRA label population (PD-L1 ≥1%). See section 3.2.3 for further details.
Outcome measures	B.2.3.1, Table 5, p.37	**Appropriate** The primary outcome was overall survival. Other outcomes were progression-free survival, objective response rate, duration of response, best overall response, quality of life and adverse effects. Whilst the company revised to trial protocol to make overall survival rather than progression-free survival the primary outcome, all relevant outcomes in the NICE decision problem were considered by the EAG to be reported adequately.
Results: Efficacy outcomes	B.2.6, pp.49-57	**Appropriate/some concerns** In the MHRA label population (PD-L1 ≥ 1%): • OS was 23.5 months vs 12.1 months in the intervention group vs placebo group (HR = 0.51, 95% CI 0.38-0.69), P<0.0001)

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
		• PFS was 8.3 months vs 5.5 months in the intervention group compared to the placebo group (HR = 0.48, 95% CI: 0.37-0.62, P<0.0001) • The ORR was 47.9% (95% CI: 41.1, 54.8) vs 22.7% (95% CI: 15.3, 31.7) in the intervention group versus the placebo group (P < 0.0001). • The duration of response was 17.5 months vs 6.5 months in the intervention group vs the placebo group (HR: 0.40, 95% CI: 0.23, 0.71, P = 0.0013). • Statistically significant differences favouring cemiplimab + chemotherapy versus chemotherapy alone were present for several function and symptom domains on the QLQ-C30 and QLQ-LC13 quality of life tools. For example, pain symptoms at data cut-off compared to baseline were -4.31 (95% CI: -8.07, -0.55) in favour of the intervention (P = 0.0248)'. However, there was a lack of statistically significant difference between comparison groups for most of the quality-of-life outcomes assessed. The EAG agrees with the company's interpretation that PFS, OS, duration of response and specific HRQoL measures demonstrated a clinically meaningful difference favouring cemiplimab with chemotherapy compared to placebo with chemotherapy. However, the results for many HRQoL measures were not statistically significant. See section 3.2.4 for further details.
Results: Adverse events	B.2.10.1, p.73 – p.74	**Appropriate/some concerns** TEAEs was similar between treatment groups with a greater incidence of grade 3 to 5 TEAEs in the cemiplimab + chemotherapy group, twenty-seven (8.7%) receiving cemiplimab + chemotherapy had TEAEs that led to death, compared to 14 (9.2%) in the placebo + chemotherapy group. Ninety-four patients (30.1%) in the cemiplimab group and 37 (24.2%) in the placebo had serious AEs (SAEs). The most common SAEs were pneumonia, anaemia and death in the cemiplimab + chemotherapy group, and febrile neutropenia in the placebo + chemotherapy group.

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
		Three patients (1.0%) in the cemiplimab + chemotherapy group discontinued and one patient died due to immune related AEs. The company submission reports that discontinuations due to immune-related AEs and AEs were low in the EMPOWER-Lung 3 trial in the context of results previously reported for other IO + chemotherapy regimens. However, [redacted] which is associated with reduced toxicity is important to note. See section 3.2.5 for further details.
Results: Subgroup analyses	Appendix E, p.93 – p.95.	**Some concerns** The company carried out all pre-planned subgroup analysis as specified in the trial protocol. In all MHRA label subgroups (squamous/non-squamous and PD-L1 1-49%/ ≥PD-L1 50%), PFS, OS, and ORR outcomes favoured cemiplimab + chemotherapy compared to placebo + chemotherapy. Whilst there were no statistically significant differences in PFS, ORR, or OS between the subgroups analysed, forest plots indicated that the benefit of conclusion in favour of placebo + chemotherapy was less amongst those aged over 65 years, females, people with an ECOG score of 1, patients with metastatic disease and brain metastasis. See section 3.2.6 for further details.

Trial design or conduct concept	Section in CS where methods are reported	EAG's assessment
Source: Company submission document B.[4], Company submission document B appendices.[8] Abbreviations: IV = intravenous; Q3W = every three weeks; AUC = area under curve; EAG = evidence assessment group; NICE = National Institute for Health and Care Excellence; PD-L1 = programmed death-ligand 1; NSCLC = non-small cell lung cancer; ECOG = eastern cooperative oncology group; ECOG PS = ECOG Performance Status; PD-L1 = Programmed death-ligand 1; EGFR = Epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; ROS = Proto-oncogene tyrosine-protein kinase; ROS 1= ROS proto-oncogene 1; ITT = intention to treat; MHRA = Medicines and Healthcare products Regulatory Agency; IO = immunotherapy; UK = United Kingdom; OS = overall survival; HR = hazard ratio; ORR = overall response rate; CI = confidence interval; GHS = global health status; EORTC = European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30 = The EORTC Core Quality of Life questionnaire; HRQOL = Health-related quality of life; PFS = progression-free survival; TEAEs = Treatment emergent adverse events; AEs = adverse events; SAEs = severe adverse events; OR = odds ratio		

3.2.1 Comparator

A breakdown of the different chemotherapy regimens used for the ITT trial population was provided by the company (CS section B.2.4, figure 4, p.48); however, a breakdown of the chemotherapy regimens used for the 4 subgroups in the MHRA label population (squamous/non-squamous, PD-L1 1-49%/PD-L1 ≥ 50%) was not provided by the company.[4]

The current chemotherapy regimens used in combination with IO treatments in UK practice are those specified in the Bluteq protocol. For non-squamous histology the chemotherapy options are pemetrexed with platinum chemotherapy, and for squamous histology, the chemotherapy regimens are carboplatin and paclitaxel.[12,13] The clinical expert advised the EAG that in UK clinical practice patients should be fit to receive AUC 6 carboplatin dose. In the cemiplimab + chemotherapy arm of EMPOWER-Lung 3, [redacted] of the participants were selected by investigators at baseline to receive an AUC 6 carboplatin dose, and [redacted] were selected to receive an AUC 5 carboplatin dose. This was to allow more flexibility in the chemotherapy regimen used and reduce the toxic side-effects of AUC 6 carboplatin. Additionally, according to the EAG's clinical advisor, the proportion of non-squamous patients receiving paclitaxel + carboplatin rather than pemetrexed was higher in the company's trial than would be expected in routine NHS care. This may reflect the increased flexibility of chemotherapy regimens in the EMPOWER-Lung 3 trial compared to clinical practice. The EAG is unable to comment on the likely impact of this deviation on trial outcomes.

3.2.2 Baseline characteristics

In the MHRA, label population, the EAG notes that the proportion of patients over 65 years was higher in the cemiplimab + chemotherapy group (40.6%) compared to the placebo + chemotherapy group (32.7%) and the proportion of females in the cemiplimab group (14.7%) was lower than the placebo group (20.0%). However, the EAG's clinical advisor was not concerned that these differences would substantially impact on conclusions.[14]

The EAG has concerns that the baseline characteristics of the trial population may differ from the NSCLC population in the UK. Amongst the MHRA label population in the trial, the median age of participants in the four subgroups was between 59.0 and 63.5 years, and the percentage aged 65 years or older was between 27.3% and 42.6%. The National Cancer Institute estimates the median age for lung cancer diagnosis to be 71 years, and in the UK patient population 45% of lung cancer patients are aged over 75 years.[15,16] This indicates the average age of those in the trial population is likely lower than the average age of the UK NSCLC population. Likewise, in all four subgroups of the MHRA label population, the proportion of male participants was >75% which was considerably higher compared to the 52% proportion of males in the UK patient population.[15]

The clinical advisor noted that brain metastasis was lower than would be expected in the UK population and the imbalance in histology types may be due to the over-representation of males in the trial who are more likely to have squamous disease.

3.2.3 Statistical analyses

The EAG has some concerns that due to the trial being powered to detect significant differences in the ITT population rather than the MHRA population, outcome differences between cemiplimab and placebo treatment groups may not have been adequately reflected. The company reported data showing that many of the HRQoL outcomes were not statistically different, albeit that pain symptoms and time to clinically meaningful deterioration were statistically different for certain measures, favouring the cemiplimab + chemotherapy group. Immunotherapies can cause immune-related adverse events that may impact on patients' HRQoL; a sufficiently powered trial may have greater ability to detect these differences. However, the EAG acknowledges that HRQoL outcomes are harder to quantify than survival outcomes.[17]

3.2.4 Efficacy outcomes

The EMPOWER-Lung 3 study was powered to the ITT population (PD-L1 any level) rather than the MHRA population (PD-L1 ≥1%) and the company noted that '*all analyses of the MHRA label population are therefore exploratory*' (CS section B.2.4.1, p.42).[4] Due to the study being underpowered, the EAG has concerns that differences in many HRQoL outcomes between patients who received cemiplimab + chemotherapy versus chemotherapy alone were not adequately detected. The EAG notes, however, that there was a significant difference in pain symptoms and a delay in time to definitive clinically meaningful deterioration favouring cemiplimab plus chemotherapy for certain functional and specific symptoms. Furthermore, the impacts of treatments on HRQoL outcomes are more difficult to quantify compared to survival outcomes, which may account for the mainly non-significant results for the effects of cemiplimab + chemotherapy compared to chemotherapy alone, on most of the HRQoL outcomes.

3.2.5 Adverse events

The safety outcomes of the EMPOWER-Lung 3 trial were comparable to other studies of immunotherapy + chemotherapy in NSCLC patients. However, these studies involved a less flexible chemotherapy regimen and required participants to receive an AUC 6 carboplatin dose. [redacted] patients in the cemiplimab + chemotherapy arm of EMPOWER-lung 3 study were selected by investigators at baseline to initiate treatment with an AUC 5 carboplatin dose which

is not routinely possible for patients with squamous disease in the UK currently as NHS commissioning policy (Blueteq protocol) mandates that patients are 'fit' to initiate treatment with AUC 6 carboplatin. The EAG's clinical advisor expressed that this should be considered when drawing comparisons between treatment related adverse events between studies as AUC 6 is associated with greater toxicity than AUC 5.

3.2.6 Subgroup Analysis

In the protocol for the EMPOWER-Lung 3 study, sub-group analyses were planned for the following variables: age, gender, race, histology, PD-L1 expression level, ECOG status, geographic region of enrolling site and ethnicity.[1] All of these analyses were undertaken; however, the company noted that: "*EMPOWER-Lung 3 was not powered to evaluate differential effectiveness in subgroups and it should be noted that interpretation of results in some subgroups is limited (e.g. by small patient numbers or by the potential for confounding owing to potential imbalances in prognostic baseline characteristics*." (CS section B.2.7, p.58).[4]

In the EMPOWER-Lung 3 study, females and patients aged over 65 years were under-represented compared to the UK patient population and the clinical expert to the EAG noted that the proportion of patients in the trial with brain metastasis was also lower than would be expected. The forest plots for OS, PFS, and ORR indicate that the treatment benefits of cemiplimab + chemotherapy may be less favourable in females, patients aged over 65, and patients with brain metastasis, but there was no statistically significant difference. The company acknowledges in their submission that the trial was not sufficiently powered for the MHRA label population (PD-L1 ≥1%) which is the population in the NICE scope, and the EAG also notes the relatively small number of females, patients aged over 65 and patients and patients with brain metastasis which preventing robust subgroup analysis. The EAG agrees with the company that the direction of treatment effect was consistent between these sub-populations; however, it does not fully support the company's conclusion that the magnitude of treatment effect was consistent. A trial with adequate numbers of patients in each sub-population would have a higher power to detect differences in treatment effects between subgroups and would be needed to confidently reach these conclusions.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company conducted an NMA to estimate the effectiveness of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy including studies that investigated these technologies compared to chemotherapy alone. A summary of the EAG's critique of the NMA is provided in **Error! Reference source not found.**.

Table 3.3: Summary of the EAG's critique of the company's indirect comparisons

Aspect of NMA design or conduct	Section in CS where methods are reported	EAG's assessment
Statistical methods	Appendix D1.1, pp. 64-89	**Appropriate** For PFS and OS, the company used a 2-step NMA approach developed by Cope et al.[19] Standard parametric models were fit to all arms of all trials

Aspect of NMA design or conduct	Section in CS where methods are reported	EAG's assessment
	Regeneron UK Limited. Data on file: Cemiplimab combination NMA report. 2024.[18]	included in the NMA. One parametric model was selected for the base case. The difference in the shape and scale parameters of this parametric model from the shape and scale parameters of the reference treatment (chemotherapy) were estimated using a fixed effect bivariate normal NMA. For adverse events and response, the company used a log-logistic model with a logit link. A fixed effect model was used. See section 3.3.1 for further details.
Included and excluded studies	Appendix D1.1, pp. 53, 55-56	**Appropriate** The exclusion of studies based on lack of NICE recommended treatments and overlapping populations is reasonable. See section 3.3.2 for further details.
Included study characteristics and demographics and transitivity assumption	Regeneron UK Limited. Data on file: Cemiplimab combination NMA report. 2024. p.108	**Key issue 3** The company reported that baseline differences between groups across included trials was not known for the target populations of their NMAs. Therefore, the potential for bias related to this could not be assessed. See section 3.3.3 for further details.
Results	Tables 78-85, Appendix D1.1, pp. 87-89 Appendix Q, pp. 195-206	**Some concerns** The company reported the hazard ratio estimates and presented survival curves with 95% confidence intervals. However, the NMA estimated the shape and scale parameters of the parametric survival curves and the results of these were not presented. See Section 3.3.4 for further details.
Subgroup analyses	Appendix D, pp. 195-206	**Some concerns** The company reported that cemiplimab + chemotherapy was of similar effectiveness to pembrolizumab + chemotherapy for all subgroups. However, the EAG note that this may not be the case for all sub-group analyses. See section 3.3.4 for further details.
Sensitivity analyses	Appendix D1.1, pp 64-89	**Appropriate** The company ran various sensitivity analyses (e.g. broader networks including more active interventions, random-effects models, constant hazard models). Results were very similar in these analyses.

Source: CS Appendix D, Section D1.1, pp.53-89; Appendix Q pp.195-206.[8] Regeneron UK Limited. Data on file: Cemiplimab combination NMA report. 2024.[18]

Aspect of NMA design or conduct	Section in CS where methods are reported	EAG's assessment
Abbreviations: EAG = Evidence Assessment Group; CS = company submission; PFS = progression-free survival; OS = overall survival; NICE = National Institute for Health and Care Excellence; NMA = Network meta-analysis		

3.3.1 Statistical methods

The EAG agreed the rationale for conducting a NMA was appropriate, given the lack of RCTs comparing the effectiveness of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy. A summary of the methods used, with the EAG's critique, is provided below.

3.3.1.1 *Two-step NMA*

NMA models for PFS and OS were conducted using a 2-step method, which allows for hazard ratios to vary over time.[19] The EAG agrees this is an appropriate method for analysing these data, since the proportional hazard assumption was likely violated for some outcomes (e.g. OS).

The first step involves fitting a standard set of parametric survival models to reconstructed individual participant data for OS and PFS for each trial arm (exponential, Gompertz, Weibull, log-normal, log-logistic, gamma and generalized gamma). The best-fitting parametric distributions were selected based on goodness of fit (AIC), plausibility of underlying assumptions, and plausibility of model fit within-trials.

The second step then uses the scale (how spread out the distribution) and shape (the shape of the distribution) parameters from the first step to estimate time-varying hazard ratios for all interventions included in the Bayesian multivariate NMA model.

3.3.1.2 *Heterogeneity and Fixed effect models*

Fixed effect models were used for all analyses as there were very few trials included in analyses. For example, base-case analyses that included all participants with PD-L1≥1% were based on four trials. The EAG agreed that there was an insufficient number of trials to model between-study heterogeneity therefore it was appropriate to use fixed effect models. However, the disadvantage is that there is no way to quantify heterogeneity, a key factor for evaluating the validity of these analyses.

3.3.2 Included and excluded studies

Thirty-seven trials were excluded due to no recommended NICE intervention. Three trials were excluded due to overlapping populations with their respective global trials, 10 studies were included (see table 3.4, below). While the exclusion of studies may lead to the exclusion of indirect evidence, given the lack of direct comparisons between active interventions, the impact on effect estimates for key comparators is likely to be minimal. Evidence networks for the base case analyses (PD-L1 ≥1%, any histology) are presented in Figure 3.1 and Figure 3.2.

Table 3.4 Trials available for each histology population

Trial	Scenario	Intervention/Comparator
R2810-ONC-16113 (pt.2)[1]		Cemiplimab + IC chemotherapy vs. IC chemotherapy (cisplatin/carboplatin + paclitaxel/pemetrexed)
KEYNOTE-024[20]		Pembrolizumab vs. IC chemotherapy (carboplatin/cisplatin + pemetrexed/gemcitabine or carboplatin + paclitaxel)
KEYNOTE-042[21]		Pembrolizumab vs. IC chemotherapy (carboplatin + paclitaxel/pemetrexed)
KEYNOTE-021G[22]		Pembrolizumab + carboplatin + pemetrexed vs. carboplatin + pemetrexed
KEYNOTE-189[23]		Pembrolizumab + IC chemotherapy vs. IC chemotherapy (cisplatin/carboplatin + pemetrexed)
KEYNOTE-407[24]		Pembrolizumab + IC chemotherapy vs. IC chemotherapy (carboplatin + paclitaxel/nab-paclitaxel)
IMpower110[25]		Atezolizumab vs. IC chemo (carboplatin/cisplatin + pemetrexed/gemcitabine)
IMpower130[26]		Atezolizumab + carboplatin + nab-paclitaxel vs. carboplatin + nab-paclitaxel
IMpower150[27]		Atezolizumab + carboplatin + paclitaxel[a] vs. atezolizumab + bevacizumab + carboplatin + paclitaxel vs. bevacizumab + carboplatin + paclitaxel[b]
PAULIEN[28]		Pembrolizumab vs. pembrolizumab + platinum chemotherapy (regimens not specified)

Reproduced from Table 4-1, page 57 in the company NMA report.[18]
Notes: *For a given trial, IC chemotherapy regimens in the immunotherapy combination arm are identical to those listed in the comparator arm. Scenario colors correspond to the following: PD-L1 ≥1%, any histology; PD-L1 1-49%, squamous histology; PD-L1 ≥50%, squamous histology; PD-L1 1-49%, non-squamous histology; PD-L1 ≥50%, non-squamous histology; PD-L1 ≥1%, squamous histology; PD-L1 ≥1%, non-squamous histology; PD-L1 1-49%, any histology; PD-L1 ≥50%, any histology; any PD-L1, any histology.* ***a)*** *Atezolizumab + carboplatin + paclitaxel is not recommended by NICE but was included to facilitate the indirect comparison with atezolizumab + bevacizumab + carboplatin + paclitaxel;* ***b)*** *Bevacizumab + carboplatin + paclitaxel was not considered to be a relevant comparator and was therefore excluded from the feasibility assessment.*
Abbreviations: *IC, investigator's choice; NICE, National Institute for Health and Care Excellence.*

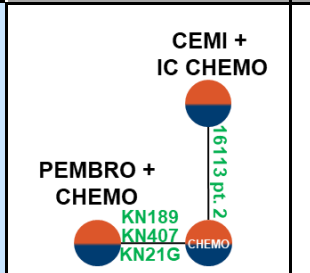
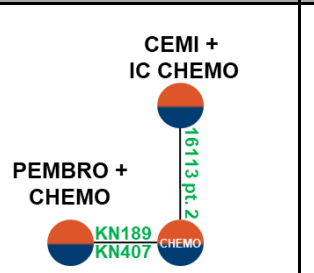
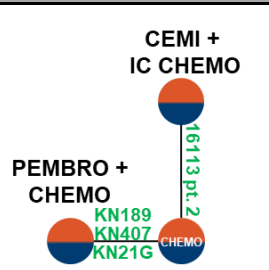
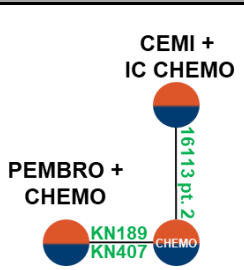
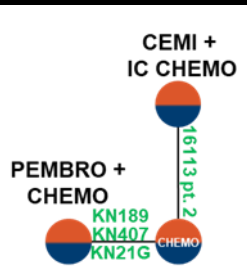
Scenario	Overall survival		Progression-free survival		ORR
	Constant HR	Time-varying HR	Constant HR	Time-varying HR	
PD-L1 ≥1%, any histology (efficacy base case)					

Figure 3.1 Reproduced from Figure 4-4, p.79 in the company NMA report:[8] evidence network diagrams for overall survival, progression-free survival and response

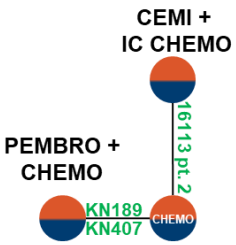
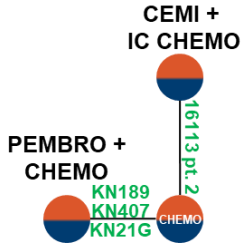
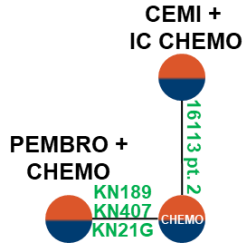
Scenario	Safety		
	Grade 3 to 5 all-cause AEs	Grade 3 to 5 IMAEs	DAEs
Any PD-L1, any histology (safety base case)			

Figure 3.2 Reproduced from Figure 4-4, p.88 in the company NMA report:[8] evidence network diagrams for safety

3.3.3 Transitivity assumption

The company acknowledge it is not possible to assess the validity of the transitivity assumption for all their NMA models. First, almost all analyses had no closed loops – which are necessary for comparison of direct and indirect evidence.

An additional difficulty is that all trials included a combination of patients with PD-L1 <1% and PD-L1 ≥1%. Since baseline characteristics were not reported according to PD-L1 status for any comparator trials, the company noted it was not possible to formally assess the transitivity assumption as the necessary baseline characteristics for key effect modifiers, in the target population, were not available.

However, it was possible to identify differences between trials for some potential prognostic factors:

- Chemotherapy regimens differed across trials (for example, trials differed in terms of provision of paclitaxel, nab paclitaxel, pemetrexed, carboplatin, cisplatin and their combinations); this variation may have impacted on effect estimates.

- Trials of pembrolizumab and chemotherapy allowed for treatment switching (but did not report data adjusted for effects of crossover). In contrast, the company's EMPOWER Lung-3 trial did not allow for treatment switching. This difference in study design may favour cemiplimab as treatment switching could dilute the treatment effect for pembrolizumab and chemotherapy. The company reported that the % of patients in the chemotherapy arms of the comparator trials who received subsequent pembrolizumab treatment was not reported at the relevant timepoints. However, 41-42% had received pembrolizumab in study crossover at 5 years in the KEYNOTE-189 and KEYNOTE-407 studies.

3.3.4 Results

3.3.4.1 *PFS and OS*

Hazard ratios at different time points for the log-logistic model are reproduced from the CS below (see Tables 3.5 and 3.6). The company produced results for the other parametric models which were similar, and consequently only reported the log-logistic results. The log-logistic model was the best fitting model according to the total AIC and BIC across the trial arms of the studies included in the NMA.

The company claimed that these analyses suggested comparable efficacy between pembrolizumab + chemotherapy and cemiplimab + chemotherapy. The EAG partially agree with these conclusions. Differences in the NMA were not statistically significant and effect estimates generally favoured cemiplimab + chemotherapy. Therefore, it is plausible that this treatment is at least as effective as pembrolizumab + chemotherapy. However, the EAG also note the 95% credible intervals were too wide to rule out important differences either in favour of pembrolizumab + chemotherapy or cemiplimab + chemotherapy. In agreement with the company, the transitivity issues mentioned in Section 3.3.3 should be considered in the interpretation of the results.

Table 3.5 OS NMA results for the PD-L1 ≥1%, any histology scenario (log-logistic, fixed effect model)

Cemiplimab + chemotherapy versus	Time-varying HR (95% CrI)							
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Pembrolizumab + chemotherapy	0.94 (0.52, 1.57)	0.90 (0.60, 1.32)	0.88 (0.62, 1.26)	0.87 (0.62, 1.26)	0.87 (0.61, 1.28)	0.87 (0.60, 1.30)	0.88 (0.60, 1.31)	0.88 (0.60, 1.32)

Reproduced from Table 4-3, page 90 in the company NMA report.[18]
Notes: *Cells shaded in light grey indicate timepoint past shortest median follow-up of treatments included in a given comparison; cells shaded in dark grey indicate estimates based on model extrapolations. The model presented is log-logistic, fixed-effect. All bolded values are statistically significant at the 0.05 significance level.*
Abbreviations: *CrI, credible interval; HR, hazard ratio.*

Table 3.6 PFS NMA results for the PD-L1 ≥1%, any histology scenario (log-logistic, fixed effect model)

Cemiplimab + chemotherapy versus	Time-varying HR (95% CrI)							
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Pembrolizumab + chemotherapy	1.09 (0.77, 1.53)	1.06 (0.79, 1.45)	1.04 (0.76, 1.45)	1.03 (0.74, 1.45)	1.02 (0.72, 1.43)	1.01 (0.72, 1.42)	1.00 (0.72, 1.40)[a]	1.00 (0.72, 1.38)[b]

Reproduced from Table 4-4, page 92 in the company NMA report.[18]
Notes: *Cells shaded in light grey indicate timepoint past shortest median follow-up of treatments included in a given comparison; cells shaded in dark grey indicate estimates based on model extrapolations. Model presented is log-logistic, fixed-effect. All bolded values are statistically significant at the 0.05 significance level.*
a) HR 1.0044 (95% CrI 0.7202, 1.3957); b) HR 1.0010, 95% CrI 0.7229, 1.3804
Abbreviations: *CrI, credible interval; HR, hazard ratio*

3.3.4.2 *Subgroup* analyses for OS and PFS

Results from the subgroup analyses (PD-L1 status, and squamous vs non-squamous) were largely similar to the base-case NMA analyses (PD-L1 ≥1%) of OS and PFS. As expected, given the smaller sample size found in subgroup analyses, the 95% CrIs were wider than in the base-case.

However, for the PD-L1 1-49% squamous group, PFS favoured pembrolizumab + chemotherapy over cemiplimab + chemotherapy (HR 1.49, 95% CrI 0.80 to 2.76, 24 month follow up), although the 95% CrI overlaps with no difference. This effect estimate is more favourable to pembrolizumab + chemotherapy than found for the base-case (PD-L1 ≥1%) PFS (HR 1.01, 95% CrI 0.72 to 1.42); however, there is overlap in 95% CrIs between the base-case (PD-L1 ≥1%) and PD-L1 1-49% squamous group. In contrast, for the PD-L1 1-49% squamous group, OS favoured cemiplimab + chemotherapy (HR 0.84, 95% CrI 0.44 to 1.60, 24 month follow up) in a similar way to the base-case.

3.3.4.3 *Adverse effects*

Cemiplimab + chemotherapy was associated with increased odds for Grade 3 to 5 all-cause adverse events, although the 95% credible interval included 1 (i.e. no difference). For Grade

3 to 5 IMAEs and discontinuation due to all-cause adverse events, 95% credible intervals were too wide to draw any conclusions. For further details, see Table 3.7, which reproduces Table 17 from the CS.

Table 3.7: Safety NMA results for the any PD-L1, any histology scenario (fixed effect)

Cemiplimab + chemotherapy versus	OR (95% CrI)		
	Grade 3 to 5 all-cause AEs	Grade 3 to 5 IMAEs	DAE
Pembrolizumab + chemotherapy	1.53 (0.95, 2.49)	1.58 (0.27, 9.78)	0.55 (0.22, 1.50)

Reproduced from Table 17, CS document B, p.70.[4]

Notes: *AE, adverse event; CrI, credible interval; DAE, discontinuation due to all-cause AEs; IMAE, immune-mediated AE; NMA, network meta-analysis; OR, odds ratio*

3.4 Conclusions of the clinical effectiveness section

The EAG had concerns regarding differences between the NICE scope and the company's decision problem in relation to the comparators and population of interest. Specifically, the company only included one comparator (pembrolizumab + chemotherapy) despite multiple treatments being included in the NICE scope. Also, the company included the PD-L1, squamous population despite the standard of care for this population sub-group being IO monotherapy. After querying both issues with the company in the PfCs and with the clinical advisor to the EAG, the EAG concludes that pembrolizumab + chemotherapy is the relevant comparator and that the PD-L1 ≥50%, squamous population sub-group is relevant in certain situations, e.g. IO + chemotherapy would be the standard of care first line treatment for this population sub-group when urgent clinical intervention is needed, including where the disease is progressing rapidly. However, the EAG has raised these as key issues, to make the NICE committee aware that cemiplimab + chemotherapy is only appropriate for administration to patients who would otherwise have received pembrolizumab + chemotherapy.

In relation to the SLR, several concerns were raised, including the exclusion of non-English studies and of phase I/ IV trials and observational studies. None of these points were identified by the EAG as being key issues; however, they are important to note.

The EAG believe the EMPOWER-Lung 3 trial was mainly conducted appropriately; however, several issues were identified. The first issue to note is that the flexibility of investigators' choice chemotherapy regimens used in the trial is not reflective of chemotherapy regimens routinely used in UK clinical practice. It is feasible that this flexibility will be allowed in clinical practice should NICE recommend the use of cemiplimab + chemotherapy; however, this issue does reduce comparability with the pembrolizumab + chemotherapy, for which there is less flexibility regarding the accompanying chemotherapy regimens. The EAG also has concerns that the trial population may not be representative of the UK patient population, with the trial sample having a younger age profile and a much smaller proportion of females compared to UK clinical practice. The EAG also has concerns in relation to the fact that the EMPOWER-Lung 3 trial was powered to the ITT population (any PD-L1 expression) and was underpowered for the MHRA label population (PD-L1 ≥1%) which is the population in the NICE scope, and how this may have impacted the detection of significant effects, particularly in sub-

group analyses and in relation to HRQOL outcomes. None of these points were identified by the EAG as being key issues; however, they are important to note.

The results from the NMA indicated comparable effectiveness between cemiplimab + chemotherapy compared to pembrolizumab + chemotherapy overall, although with very wide credible intervals. The EAG noted greater uncertainty around the effectiveness of cemiplimab + chemotherapy in the PD-L1 1-49%, squamous sub-group for PFS as the estimate favoured pembrolizumab + chemotherapy in this population, again with very wide credible intervals. The transitivity assumption could not be assessed using statistical methods as there were no closed loops within the NMA network to enable comparisons between direct and indirect evidence for the effectiveness of cemiplimab + chemotherapy versus pembrolizumab versus chemotherapy. Furthermore, there was a lack of information regarding the degree of homogeneity in relation to the PD-L1 status of patients within each trial. Additionally, patients in the pembrolizumab + chemotherapy trials were allowed to switch between treatment after disease progression, which was not the case in the EMPOWER trial of cemiplimab, resulting in an unknown percentage of patients receiving immunotherapy in the control arms of the pembrolizumab trials by the data cut timepoint for the NMA analyses in the CS. This may affect the OS hazard ratio time-varying estimates. Variations in the chemotherapy regimens received by patients in each trial were also apparent. These issues introduce uncertainty into the NMA results as they undermine the comparability of trials within the network. The EAG has identified this as a key issue.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

This section pertains mainly to the review of cost-effectiveness analysis studies. However, the search section also contains summaries and critiques of other searches related to cost-effectiveness presented in the company submission. Therefore, the following section includes searches for the cost-effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

Table 4.1 presents an overview of the EAG's critique of the methods used to identify studies for the review of cost-effectiveness.

Table 4.1: Summary of the EAG's critique of the methods for the review of cost-effectiveness

Aspect of cost-effectiveness SLR	Section in CS where methods are reported	EAG's assessment
Data sources for cost-effectiveness analysis review	Appendix G, Appendix H, Appendix I	**Appropriate** Two parallel systematic reviews were carried out by the company in January 2020, with updates in January 2021, May 2022, and May 2024. The May 2024 update had a UK specific focus while the earlier reviews were conducted with a global scope. Given the rapidly evolving treatment landscape, a date restriction of the year 2009 was applied to the main database searches. The first systematic review focussed on published cost-effectiveness/cost-utility analyses and health resource utilisation, whilst the second systematic review focussed on HRQoL studies. An appropriate range of electronic bibliographic databases and HTA websites were searched. These main database searches were augmented with a search of specific conference proceedings, grey literature and supplementary hand-searching. Relevant citations identified through the conference proceedings were also checked for additional relevant studies. The second systematic review focussed on Health-related quality-of-life studies. The review methods were almost identical to the systematic review on cost-effectiveness/cost-utility analyses and health resource utilisation, with the exception that HTA body hand-searches were not performed as relevant data was assumed to be captured via the inclusion of HSUV data in the HTA body hand searches performed as part of the economic SLR.
Search strategies	Appendix H, 1.1, p. 128-148	**Appropriate** The search strategies used to find cost-effectiveness studies were fit for purpose.

Aspect of cost-effectiveness SLR	Section in CS where methods are reported	EAG's assessment
Search filters	Appendix H, 1.1, p 128-148	**Some concerns** The EAG is concerned that the HRQoL study type filter has been altered, potentially making the filter less sensitive. Please see Section 4.1.1 for further comment.
Data sources for model input	Appendix G, Appendix H, Appendix I	**Appropriate** Nineteen economic evaluation studies with UK relevant data were identified as part of the SLR and subsequent updates, including nine previous NICE technology appraisals. Seven alternative HSUV sources were identified in the SLR.
Eligibility criteria for inclusion of economic evaluations	Appendix G, 1.1, Table 95	**Appropriate** The eligibility criteria were appropriate to capture cost-effectiveness studies in this area.
Eligibility criteria for inclusion of health state utility value studies	Appendix H, 1.1, Table 98	**Appropriate** The eligibility criteria were appropriate to capture quality of life in this area.
Eligibility criteria for inclusion of resource use and cost studies	Appendix G, 1.1, Table 95	**Appropriate** The eligibility criteria were appropriate to capture resource use and costs in this area.

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; HTA = health technology assessment; HSUV = health-state utility values; SLR = systematic literature review; NICE = National Institute for Health and Care Excellence

4.1.1 Search filters

The company conducted separate searches for clinical effectiveness studies.[8] The EAG used the PRESS checklist to appraise the search strategies.[9]. The HRQoL study type filter used by the company came from the Canadian Agency for Drugs and Technologies in Health (CADTH).[10,29] On closer inspection, the EAG identified that the original HRQoL study type filter had been modified, excluding MeSH terms, keywords and using different search fields. The company did not provide a rationale for the alteration from the original filter or report this alteration in the search methods. This would make the filter less sensitive and impact locating relevant studies. However, no terms were missing from both MeSH and keywords and so the overall impact on the retrieved studies is likely to be relatively small.

4.1.2 Conclusions of the cost effectiveness review

The SLR conducted by the company found a total of 19 economic evaluation studies containing UK relevant data, including nine previous NICE technology appraisals. The data identified in the SLR informed the overall model structure used by the company and several other inputs for the CEM. Although the EAG has some concerns regarding the HRQoL study

type filter used by the company, overall is satisfied that the cost effectiveness review has been conducted appropriately.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.2 summarises the NICE reference case checklist and the EAG's assessment on the company's submission in relation to their base-case analysis.

Table 4.2: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	Cemiplimab with chemotherapy for adults with untreated locally advanced (which is not a candidate for definitive chemoradiation) or metastatic NSCLC which expresses PD-L1 on 1% or more of tumour cells and has no EGFR, ALK or ROS-1 genetic alterations.	**Key Issue 1** The population who would be eligible to receive cemiplimab + chemotherapy is a subset of the NICE scope. The EAG consider this to be a key issue in the CS. See section 2.1 for further details.
Comparators	For people with squamous NSCLC whose tumours express PD-L1 on 1 to 49% of tumour cells: • Platinum doublet chemotherapy • Pembrolizumab with carboplatin and paclitaxel For people with squamous NSCLC whose tumours express PD-L1 on 50% or more of cells: • Platinum doublet chemotherapy • Pembrolizumab monotherapy • Atezolizumab monotherapy	**Key issue 2** The company only included one comparator (pembrolizumab + chemotherapy) in their decision problem, despite various other treatment options being available in the NICE scope and clinical pathways for the population of interest. The EAG consider this to be a key issue in the CS. See section 2.2 for further details.

Element of health technology assessment	Reference case	EAG comment on company's submission
	• Pembrolizumab with carboplatin and paclitaxel (for people in need of urgent clinical intervention) For people with non-squamous NSCLC whose tumours express PD-L1 on 1 to 49% of tumour cells: • Pembrolizumab with pemetrexed and platinum chemotherapy • Atezolizumab with bevacizumab, carboplatin and paclitaxel • Pemetrexed with platinum doublet chemotherapy For people with non-squamous NSCLC whose tumours express PD-L1 on 50% or more of cells: • Pembrolizumab with pemetrexed and platinum chemotherapy • Pembrolizumab monotherapy • Atezolizumab monotherapy • Pemetrexed with platinum doublet chemotherapy	
Perspective on outcomes	• Progression-free survival • Response rates • Overall survival • Adverse effects of treatment	**Appropriate** The EAG considers the perspective on outcomes to be appropriate.

Element of health technology assessment	Reference case	EAG comment on company's submission
	• Health-related quality of life	
Perspective on costs	NHS and personal social services (PSS)	**Appropriate** The EAG considers the perspective on costs was adequately captured.
Type of economic evaluation	Cost-utility analysis with a fully incremental analysis	**Some concerns** The company presented a CUA with a fully incremental analysis; however, they also presented a cost-comparison analysis (assuming equivalent clinical outcomes) as an alternative base case.
Time horizon	Long enough to reflect all important differences in costs and outcomes between the technologies being compared	**Appropriate** A 30-year time horizon was used for the cost-effectiveness analysis. This was considered to be appropriate given the baseline median age of the target population.
Synthesis of evidence on health effects	Based on a systematic review	**Key issue 3** In the absence of head-to-head trials of cemiplimab + chemotherapy vs relevant comparators, an NMA was conducted. The EAG identified several issues with this NMA, including the uncertainty of the effectiveness of cemiplimab + chemotherapy in the PD-L1 1-49%, squamous sub-group, the fact that the transitivity assumption could not be assessed, the lack of information regarding the degree of homogeneity in relation to the PD-L1 status of patients within each trial, the difference in the extent of treatment switching between trials and the variations in the chemotherapy regimens received by patients in each trial. The EAG consider this to be a key issue in the CS. See section 3.3.3 for further details.

Element of health technology assessment	Reference case	EAG comment on company's submission
Measuring and valuing health effects	Quality of life to be presented in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	**Some concerns** Data on quality of life was gathered from EORTC-QLQ C30 collected in EMPOWER-Lung 3 mapped to the EQ-5D-3L. The use of mapping algorithms introduces additional uncertainty into the estimates of quality of life for the different health states included in the model. See Section 4.2.6 for further details.
Source of data for measurement of health-related quality of life	Reported directly by the patients or carers or both.	**Appropriate** Reported directly by patients in the EMPOWER-Lung 3 trial.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	**Appropriate** EQ-5D values were scored in accordance with current NICE guidelines.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	**Appropriate** No decision modifiers were applied on the results.
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.	**Appropriate** Costs and resource use sourced from NHS reference costs, PSS,[30] BNF,[31] eMIT[32] and previous NICE technology appraisals in this clinical area consistent with the NICE perspective. Due to the lack of information in the EMPOWER-Lung 3 trial,[1] information regarding the duration of subsequent treatments were based on estimates reported in Insinga et al. (2021).[33] The EAG consider this source to be appropriate.
Discounting	The same annual rate for both costs and health effects (3.5%)	**Appropriate** Discounting of costs and outcomes was in line with NICE guidelines.

Element of health technology assessment	Reference case	EAG comment on company's submission
Source: CS Section B.3.6, Table 62 Abbreviation: EAG = Evidence Assessment Group; CS = company submission; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PSS = Personal Social Services; QALY = quality adjusted life-year; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand-1; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; ROS-1 = ROS proto-oncogene 1; CUA = cost utility analysis; BNF = British National Formulary; eMIT = Drugs and pharmaceutical electronic market information tool; QLQ C30 = The EORTC Core Quality of Life questionnaire		

4.2.2 Model design and assumptions

The company cost-effectiveness model (CEM) is reproduced in Figure 4.1. The company CEM was based on a 'time-in-state' strucuture (otherwise known as a 'partitioned survival model' (PSM) or 'area under the curve (AUC) model'). This is a common model used in NSCLC, and is the approach used in the majority of the prior NSCLC NICE appraisals. Patients begin in the pre-progression health state, where they receive either cemiplimab or a relevant comparator treatment and are progression-free. Patients then transition to the death state over time, or to the post-progression health state, where they receive subsequent treatment. Patients who transition to the post-progression state then move to the death state over time. The proprtion of patients in the pre-progression health state reduces over time according to hazard rates at which patients leave this state, which corresponds to PFS. The proportion of patients who died increases over time according to death rates corresponding to OS. The difference between the proportion of patients alive and the proportion of patients in the pre-progression health state represents the proportion of patients in the post-progression health state.

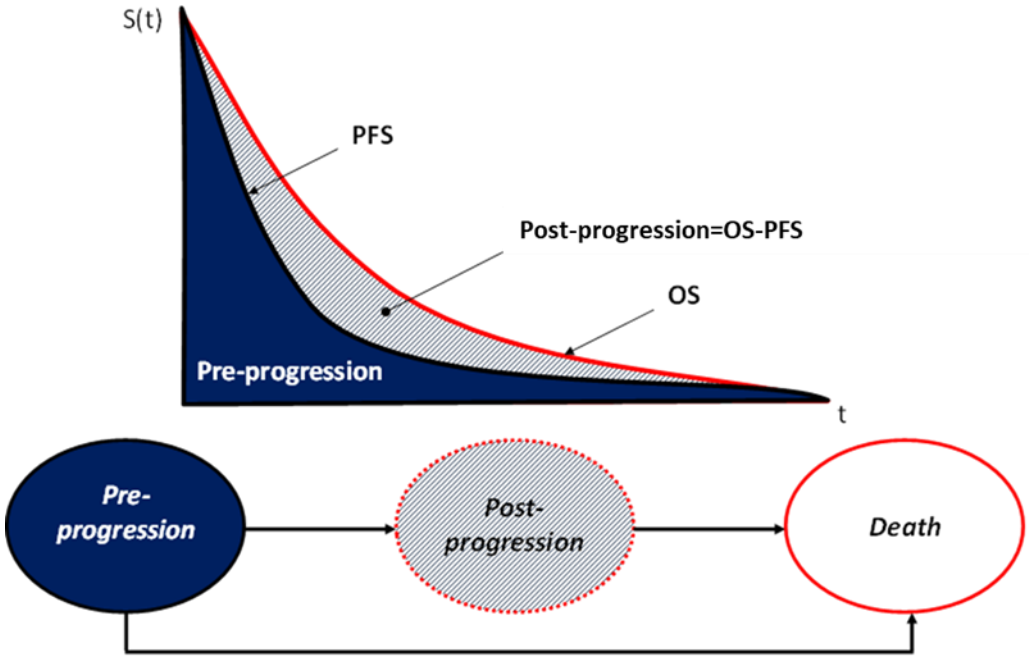


Figure 4.1: Model structure
Source: CS Document B, section B.3.2.1, Figure 14
Abbreviations: CS = company submission

Error! Reference source not found. Table 4.3 summarises the EAG's critique on the model structure adopted by the company.

Table 4.3: Summary of EAG's critique on the design of the economic model

Analysis feature	Section in CS where methods are reported	EAG's assessment
Type of model	Section B. 3.2.1, p.95	**Appropriate** A PSM was used, a structure which aligns with the vast majority of prior NSCLC NICE appraisals. There are several well-known potential issues with the use of PSMs (principally that PFS and OS are modelled independently despite being inherently linked); however, the company have clearly noted these limitations in their submission. The EAG considers the model structure to be appropriate.
Treatment effectiveness	Section B.2.9, p.61	**Key Issue 3** In the absence of a head-to-head RCT, the company used the evidence from the NMA to derive estimates of relative treatment effects between cemiplimab + chemotherapy and pembrolizumab + chemotherapy.

Analysis feature	Section in CS where methods are reported	EAG's assessment
		Specifically, the relative treatment effects from the NMA are "anchored" onto the estimates of PFS/OS in the reference arm. As discussed in Section 3.3, the EAG considers the uncertainty surrounding the NMA to be a key issue in the CS; however, the EAG considers the methods used to integrate the results from the NMA into the CEM to be appropriate.
Time-to-event analysis and extrapolation methods	B.3.3.1, p.102	**Appropriate** A standard set of parametric survival models were fit to the OS/PFS data for the chemotherapy reference arm to extrapolate treatment effects for cemiplimab + chemotherapy and pembrolizumab + chemotherapy. To select the most appropriate model, the company used both technical and clinical validation, including the total AIC across all trial arms included in the NMA. See section 4.2.3 for further details. The EAG is satisfied that the time-to-event analysis itself has been conducted appropriately, however has some concerns related to the baseline characteristics of the NMA trials which form part of the validation for model selection. See section 3.3.3 for further details.
Treatment discontinuation	Section B.3.5.1, p.161	**Key Issue 4** In the base case CEM, the company assumes that TTD is equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy, implying that all patients remain on treatment until they progress. The EAG has some concerns regarding these estimates for TTD. See section 4.2.4 for further details.
Treatment waning assumption	Section B.3.3.3, p.131	**Key issue 5** In the company base case, the treatment effect was assumed to last five years (three years beyond the two-year stopping rule), with the hazards for cemiplimab + chemotherapy and pembrolizumab + chemotherapy assumed to be equal to chemotherapy (HR=1) at the end of the fifth year. The EAG consider this 'immediate waning' of the treatment effect to be a strong assumption. The EAG regard the treatment waning assumption as a key issue in the CS. See section 4.2.5Treatment waning assumption for further details.

Analysis feature	Section in CS where methods are reported	EAG's assessment
Model predictions		**Appropriate** The company validated their model assumptions with an advisory board and externally validated their model predictions on appropriate data. The EAG is satisfied with this approach. See Section 4.2.3 and Section 5.4.2 for further details.

Source: EAG output
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence; TA = technology appraisal; PSM = Partitioned Survival Model ; NSCLC = non-small cell lung cancer; PFS = progression free survival; OS = overall survival; RCT = randomised controlled trial; NMA = network meta-analysis; CEM = cost-effectiveness model; TTD = time to death; HR = hazard ratio

4.2.3 Time to event analysis and extrapolation methods

The PFS and OS survival curves were estimated using a 2-step NMA (see section 3.3). The first part involved fitting a standard set of parametric survival models to the OS/PFS data for each trial arm in the studies included in the NMA: exponential, Gompertz, Weibull, log-normal, log-logistic, gamma and generalized gamma. More flexible models were not considered. The second part involved conducting an NMA with the transformed shape and scale parameter estimates and standard errors.

To select the most appropriate model for use in the economic model, the company used both technical and clinical validation, including:

- Statistical goodness of fit based on Akaike's information criterion (AIC) and Bayesian information criterion (BIC)
- Visual goodness of fit
- Compatibility of parametric model fit to reference curve and NMA model
- Base-case NMA model
- External validation of OS data
- Validation of extrapolations by UK clinical expert lung oncologists
- Relationship between PFS and OS
- General mortality

For PFS, the company chose the log-logistic model in the base-case, on the basis that the model had the best fit to the chemotherapy hazards, best statistical goodness of fit to chemotherapy, was the favoured NMA model and had plausible survival projections. Figure 4.2 shows the various parametric fits for PFS for the chemotherapy arm from the EMPOWER-Lung 3 trial, and Table 4.4 shows the validation summary for the PFS model selection.

Figure 4.2 EMPOWER-Lung 3 chemotherapy PFS parametric fits

Table 4.4 Validation summary table for PFS model selection

Model	NMA Model	Goodness of Fit			Two-year PFS estimates			Decision
		AIC	BIC	Total AIC across NMA	Chemo (reference)	Cemi+ chemo	Pembro + chemo	
Exponential	Deprioritized	569.23	571.93	6,649.02	4.1%	22.8%	24.5%	Deprioritized
Weibull	Deprioritized	566.12	571.52	6,629.87	2.1%	21.9%	17.8%	Deprioritized
Gompertz	Deprioritized	571.23	576.63	6,546.04	4.1%	24.3%	19.8%	Deprioritized
Log-normal	**Favoured** (second lowest total AIC)	**559.03**	**564.44**	6,519,42	5.0%	23.1%	**25.0%**	Scenario
Log-logistic	**Favoured** (lowest total AIC)	**552.73**	**558.13**	**6,488.58**	**4.8%**	21.5%	23.1%	**Base Case**
Gamma	Deprioritized	562.51	567.91	6,638.30	2.0%	21.3%	24.7%	Deprioritized
Generalised gamma (fixed Q)	**Favoured** (third lowest total AIC)	559.25	564.65	6,520.00	5.1%	**23.2%**	**25.0%**	Deprioritized

Source: CS Table 34, p.119
Abbreviations: PFS = progression-free survival; AIC = Akaike information criterion; BIC = Bayesian information criterion; NMA = network meta-analysis

Table 4.5 Validation summary table for OS model selection

Model	NMA Model	Goodness of Fit			Five-year OS estimates			Decision
		AIC	BIC	Total AIC across NMA	Chemo (reference)	Cemi+ chemo	Pembro + chemo	
Exponential	Excluded due to PH violations'	602.89	605.59	6,995.24	3.7%	17.2%	11.9%	Excluded
Weibull	Deprioritized	602.61	608.01	6,951.62'	1.8%	11.9%	6.5%	Deprioritized
Gompertz	Favoured (second lowest AIC)	603.71	609.11	6,928.61	0.8%	5.7%	3.4%	Deprioritized
Log-normal	Deprioritized	610.18	615.58	6,958.01	9.4%	25.0%	19.8%	Deprioritized
Log-logistic	**Favoured** (lowest total AIC)	604.20	609.60	6,925.18	8.4%	21.5%	17.6%	**Base case**
Gamma	Deprioritized	602.52	607.92	6,957.13	2.2%	13.6%	9.2%	Deprioritized
Generalised gamma (fixed Q)	**Favoured** (third lowest total AIC)	603.44	613.54	6,933.79	5.3%	19.5%	14.6%	Scenario

Source: CS Table 40, p.128-129
Abbreviations: OS = overall survival; AIC = Akaike information criterion; BIC = Bayesian information criterion; NMA = network meta-analysis

As shown in Table 4.4, for PFS the Log-logistic distribution had the lowest AIC and BIC and best fit to the chemotherapy hazards (4.8%) based on the landmark survival at two years from the EMPOWER-Lung 3 trial. It also had the lowest total AIC and BIC across all trial arms included in the NMA. It is worth noting that the Generalized gamma model had both the third lowest AIC and BIC and most accurate estimates of two-year PFS based on the landmark survival at two years for both cemiplimab + chemotherapy (23.2%) and pembrolizumab + chemotherapy (25.0%) from the EMPOWER-Lung 3 trial[1] and KEYNOTE-189[34] and KEYNOTE-407[35] respectively. Whilst the log-logistic distribution is retained by the EAG in the EAG base case, as part of the additional EAG analysis, the EAG have included an additional scenario analysis using the Generalized gamma model for PFS.

For OS, the company chose the log-logistic distribution in the base case, on the basis that it was the favoured NMA model, had “AIC/BIC similarity” and had plausible survival projections. **Error! Reference source not found.** shows the various parametric fits PFS for the chemotherapy arm from the EMPOWER-Lung 3 trial, and **Error! Reference source not found.Error! Reference source not found.** shows the validation summary for the PFS model selection. As shown in **Error! Reference source not found.**, for OS the log-logistic distribution had the 5th lowest AIC and the 5th lowest BIC. The Table 36 of the CS, the company present the total AIC across the OS NMA models and use these figures (in which the AIC across all study treatment arms were summed) to justify the use of the log-logistic distribution in the base case. Despite being having the lowest AIC and second lowest BIC, the Gamma model was “deprioritised” because of the summed AIC. The log-logistic distribution has been retained by the EAG in the base case, however the EAG have included an additional scenario analysis using the gamma model for OS. Overall, the EAG are satisfied that the survival analysis has been conducted appropriately.

Figure 3: EMPOWER-Lung 3 chemotherapy OS parametric fits

4.2.4 Treatment discontinuation

The EMPOWER-Lung 3 protocol allowed patients to continue treatment beyond disease progression under certain conditions, with an estimated HR compared to PFS of 1.17. As shown in Table 4.6, the corresponding HR for pembrolizumab was 0.84, calculated from the KEYNOTE-407 and KEYNOTE-189 trials and weighted by the split of squamous and non-squamous patients in EMPOWER-Lung 3.

Table 4.6: Hazard ratios available to estimate time on treatment in the model

Treatment	Estimated hazard ratio	Source
Cemiplimab + chemotherapy	1.17	EMPOWER-Lung 3
Pembrolizumab + chemotherapy	0.84	KEYNOTE 407 and KEYNOTE 189, split by squamous and non-squamous in EMPOWER-Lung 3
Source: CS Document B, Table 53		

In the base case analysis, the company assume that the ToT was equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy, guided by an advisory board meeting where advisors were cautious about concluding discrepancies between the between

cemiplimab + chemotherapy and pembrolizumab + chemotherapy treatment arms, suggesting that *"these differences might be due to IO experience bias or reporting variations between trials"*.

The EAG note that assuming that ToT is equal to PFS ignores the fact that ToT has an impact on PFS and OS, and that for consistency with the effectiveness estimates the ToT estimates should either be estimated from the respective clinical trials (EMPOWER-Lung 3 and KEYNOTE-407) or should assumed to be equal. Assuming that ToT is equal PFS will underestimate the costs for cemiplimab + chemotherapy and overestimate the costs for pembrolizumab + chemotherapy. The company included a scenario analysis where the estimated individual hazard ratios for the different treatment arms shown in Table 4.6 were used, which changed the incremental cost from [redacted] in the base case to [redacted]. The EAG have explored alternative assumptions regarding ToT as part of the EAG analysis/base case.

4.2.5 Treatment waning assumption

As stated in the CS, patients in the EMPOWER-Lung 3 trial[1] and the KEYNOTE-407[35] and KEYNOTE-189[34] trials received cemiplimab and pembrolizumab for a maximum of 24 months. To model the treatment effect beyond this 24-month period, the company assumed that there was a continuation of the treatment effect from 24 months to 60 months, after which the estimated hazard of death is assumed to be equal to chemotherapy at five years for both PFS and OS. The company justified this assumption by stating that UK clinical experts consulted by the company would expect patients to continue to experience treatment benefit following two years of IO treatment, with T-cell activation through three to five years. Furthermore, the company referenced two previous NICE appraisals for pembrolizumab + chemotherapy (TA683[36] and TA770[37]) in which treatment continuation was discussed. In TA683 a linear treatment waning from three to five years was accepted by the NICE committee, and in TA770 the committee accepted a treatment effect lasting to five years based on five-year follow up from KEYNOTE-407.

The company included three sensitivity analyses related to the waning of the treatment effect (Scenario 5, Scenario 6 and Scenario 7):

- Scenario 5 applies a linear treatment waning effect to PFS/OS from 36 months rather 60 months, reducing the incremental QALYs from [redacted] to [redacted] and changing the incremental costs from [redacted] to [redacted]
- Scenario 6 applies a linear treatment waning effect to PFS/OS starting at 36 months and ending at 60 months, reducing the incremental QALYs from [redacted] to [redacted] and changing the incremental costs from [redacted] to [redacted]
- Scenario 7 assumes a continuation of the treatment effect (no treatment waning), increasing the incremental QALYs from [redacted] to [redacted] and changing the incremental costs from [redacted] to [redacted].

The EAG is concerned that the assumption of an 'immediate' waning after five years in the company base case is overestimating the treatment benefit of both cemiplimab and pembrolizumab. As noted by Taylor et al. (2024),[38] the assumption of applying a waning on this 'immediate' basis

is that the treatment effect will disappear on a specific day, which is highly unlikely to reflect the underlying biology of the disease or the mechanism of action for IOs. Therefore, this approach appears to lack face validity and does not accord with the (albeit limited) clinical evidence. The EAG is of the opinion that applying a 'gradual' waning effect is more realistic. As noted by the company, in TA683 clinical input highlighted that a 'gradual' waning could be more clinically plausible.

As part of the EAG base case, the EAG have implemented a gradual linear waning effect for both PFS and OS starting at 24 months (in line with the stopping rule for both cemiplimab and pembrolizumab) and ending at 60 months, after which the hazard of cemiplimab + chemotherapy and pembrolizumab + chemotherapy is assumed to be equal to the hazard for chemotherapy (HR vs chemotherapy = 1), in line with the assumptions made by the company in their base case. Like the company, the EAG has applied the same assumption for both cemiplimab and pembrolizumab. Using this 'gradual' treatment waning ensures that the continuation of treatment benefit due to T-cell activation is represented in the CEM but avoids the assumption of an 'immediate' treatment waning effect. The EAG are aware that, like the assumption of an 'immediate' waning effect, the assumption of a linear gradual waning effect is not evidence based and is unlikely to truly represent the underlying biology or disease or mechanism of action.[39] Further sensitivity analysis surrounding this assumption are presented as part of the EAG analysis.

4.2.6 Health-related quality of life

Table 4.7 summarises the EAG's critique on HRQoL within the economic model.

Table 4.7: Summary of EAG's critique on HRQoL

Analysis feature	Section in CS where methods are reported	EAG's assessment
HRQoL evidence used for health states in CEM	Section 3.4.1, p.139	**Some concerns** The EAG have some concerns around the utility values used in the CEM, in particular relating to the inherent uncertainty related to the use of mapping, the population used to map to the EQ-5D and the lack of scenario analysis. See Section 4.2.6.1 for further details.

Analysis feature	Section in CS where methods are reported	EAG's assessment
Disutility for adverse effects	Section 3.4.5, p.154	**Some concerns** The disutility values for the AEs included in the CEM were identified from targeted reviews of previously published economic evaluations and HTA submissions. The EAG has some concerns regarding the AE data used in the CEM. See Section 4.2.6.2 for further comment.
Source: EAG outputs Abbreviations: AEs = adverse events; CEM = cost-effectiveness model; CS = company submission; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; AE = Adverse event		

4.2.6.1 HSUVs for the PF and PD health states

HSUVs were included in the CEM for the PF and PD health states (Table 4.8). The company assumed that because quality of life was linked to disease progression rather than treatment received, pooled values were used rather than treatment-specific utilities. Utility values were adjusted for age and sex using the approach suggested by Hernandez et al. (2022).[40] This was considered to be appropriate by the EAG.

Table 4.8: Utility values used in the CEM

Health states	Modelled average, mean (SE)
Progression-free	0.765 (0.005)
Progressed disease	0.723 (0.010)
Source: CS Document B, Table 44 Abbreviations: CEM = company economic model; SE = standard error	

As the EQ-5D was not collected in the EMPOWER-Lung 3 trial,[1] base case HSUVs were mapped from the oncology-specific EORTC-QLQ C30 using the algorithm from Longworth et al (2014),[41] which was identified by the company as being the most favourable out of those identified as part of a SLR. Although not explicitly stated in the CS, the EAG assumes that the response mapping algorithm from Longworth et al (2014) was the specific algorithm used. The EAG note that the specific choice of mapping algorithm from Longworth et al (2014) is unlikely to significantly impact the results. The mapping analysis was conducted using the EMPOWER Lung-3 ITT population (any PD-L1, any histology) population rather than the restricted population for which cemiplimab has a UK marketing authorisation (PD-L1 >1%, any histology), as the company argued that this allowed the use of all available data. The EAG note that this population does not align with the decision problem, although the impact on the results is likely to be minimal.

More generally, one of the principal limitations of predicting utility scores through mapping algorithms is that the predictive accuracy of the algorithm will be limited by the level of overlap between the two instruments in terms of what they attempt to measure. Given the significant differences between the condition-specific EORTC-QLQ C30 and the generic EQ-5D-3L, there is a degree of uncertainty related to the mapped utility estimates that remains unresolved.

Three alternative HSUVs available in the CEM are presented in Table 4.9. In the CS, the company state that sensitivity of the model to different utility values was tested by conducting scenario analyses using alternative published utility values. However, in the CS only the alternative utility values from TA584[42] are presented in as part of the scenario analysis, with the company arguing that *"only the utilities from Impower 150 are provided in Section B.3.8.3 as the other utility values from Table 44 also resulted in dominance for cemiplimab + chemotherapy"*. The EAG note that whilst the alternative utility values do result in dominance for cemiplimab + chemotherapy, the cost-effectiveness results presented in the CEM are not appropriate for decision making, as PAS prices are used for cemiplimab only, with list prices for other immunotherapies and chemotherapies. The EAG note that using the Nafees (2008)[43] utility values from TA584 has a significant impact on incremental QALYs, decreasing from [redacted] in the base case to [redacted]. The use of these alternative HSUVs is explored as part of the EAG scenario analysis.

In the CS, the company state that although four further sources were found during their SLR, these were not included in the cost-effectiveness analysis as they were from monotherapy studies *"which were indicated by UK clinical expert lung oncologists to be less representative of expected HSUV of IO + chemotherapy treatments"*. The EAG note that in the post-advisory board clarification questionnaire follow up provided in response to the PfCs,[5] Clinician 1 indicated that [redacted], however Clinician 2 and Clinician 3 indicated that [redacted]. The use of alternative utility values from IO monotherapy appraisals will be explored as part of the EAG analysis.

Table 4.9: Alternative HSUVs available in the CEM

Source	Response Status	Modelled average, mean (SE)
NICE TA584	Progression-free	0.710 (0.005)
	Progressed	0.690 (0.015)
NICE TA584 (Scenario Analysis)	Progression-free	0.673 (0.070)
	Progressed	0.473 (0.022)
NICE TA584 (Scenario Analysis)	Progression-free	0.710 (0.023)
	Progressed	0.670 (0.041)

Source: CS Document B, Table 44
Abbreviations: HSUVs = health-state utility values; TA = technology appraisal; CEM = company economic model; SE = standard error; CS = company submission

4.2.6.2 Disutility values for AEs

The disutility values for AEs used in the CEM are shown in Table 4.10. Frequencies of AEs were sourced from the EMPOWER-Lung 3 trial[1] for the cemiplimab + chemotherapy arm and the KEYNOTE-189[34] and KEYNOTE-407[35] trials for the pembrolizumab + chemotherapy arm (Table 4.11.11).

Table 4.10: Disutility values for AEs used in the CEM

Adverse event	Disutility	Source	Estimated QALY decrement
Anaemia	-0.125	Lloyd et al. (2008)[44], TA724[45]	-0.010
Fatigue	-0.073	Nafees et al. (2008),[43] TA724[45]	-0.006
Neutropenia	-0.090	Nafees et al. (2008),[43] TA724[45]	-0.007
Thrombocytopenia	-0.108	TA359[46] TA772[47]	-0.009

Source: CS Document B, Table 48
Abbreviations: CS = company submission; CEM= company economic model; AEs = adverse events; QALY = Quality-adjusted life year; TA = technology appraisal

Table 4.11: Proportions of AEs used in the CEM

Adverse event	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy
Anaemia	10.90%	17.65%
Fatigue	2.88%	6.38%
Neutropenia	6.41%	19.46%
Thrombocytopenia	3.21%	8.48%

Source: CS Document B, Table 43
Abbreviations: CS = company submission; CEM= company economic model; AEs = adverse events

The CEM assumed a 30-day duration to estimate the QALY decrement in line with the length of the model cycle, with these QALY decrements applied as a one-off decrement in the first cycle of the analysis. Although this assumption implies that all AEs are transitory (and that there are no persisting impacts of AEs on individuals over time), this is an assumption typically made in NICE TAR appraisals, for example TA802.[48] The EAG note that treatment-specific AE profiles are used in the CEM, despite the chemotherapy backbone regime being assumed to be the same across treatments. The clinical expert consulted by the EAG noted that the Grade 3+ AEs included in the model would almost exclusively be caused by the chemotherapy regime rather than IO. As noted by the company, this results in a "misalignment" between the AEs and chemotherapy regime. The company explored the impact of different AE regimes in their scenario analysis, with Scenario 13 (which excludes AE costs and disutilities) showing to have a small impact on the results. In the EAG base-case, the AEs are equalised across the treatment arms to avoid this

"misalignment". This also aligns with the clinical expert advice gathered by the company, which stated that [redacted] and that there was [redacted].

4.2.7 Resources and costs

Table 4.12.12 summarises the EAG's critique on resources and costs within the economic model.

Table 4.12: Summary of EAG's critique on resources and costs

Analysis feature	Section in CS where methods are reported	EAG's assessment
Drug acquisition costs	B.3.5.1, p.154	**Some Concerns** Drug acquisition and vial costs for all interventions were sourced from the BNF[31] and eMIT.[32] Concomitant medications and vial sharing were not included in the base-case; however, both have negligible impact on the cost effectiveness results. The EAG has some concerns regarding the distribution of chemotherapy regimes, as these were assumed to be the same for cemiplimab + chemotherapy and pembrolizumab + chemotherapy. See Section 4.2.7.1 for further details.
Administration costs	B.3.5.2, p.162	**Appropriate** Administration unit costs were sourced from the NHS reference costs[30] and applied to each treatment option in the model based on administration frequency and duration of time for delivering the regimen. The EAG find these assumptions to be appropriate.

Analysis feature	Section in CS where methods are reported	EAG's assessment
Subsequent treatment costs	B.3.5.3, p.163	**Some Concerns** Following progression on first-line treatment, subsequent therapy costs were applied for patients in the post-progression health state. The EAG has some concerns regarding these subsequent treatment costs. See Section 4.2.7.2 for further details.
Routine care costs	B.3.5.4, p.167	**Appropriate** Resources and costs for routine disease management in the pre- and post-progression health states were also included in the CEM. The frequency of resource use was sourced from NICE TA531,[49] with the unit costs sourced from NHS reference costs and PSSRU unit costs.[30] Resource use was assumed to be identical for all therapies, and validated by UK clinical experts. The EAG find these assumptions to be appropriate.
End-of-life costs (terminal care costs)	B.3.5.5, p.169	**Appropriate** A one-off cost for end-of-life care was applied upon transition to the death health state, using assumptions from TA531 and costs from the PSSRU and NHS reference costs. The EAG considers these assumptions to be appropriate.

Analysis feature	Section in CS where methods are reported	EAG's assessment
Adverse event costs	B.3.5.6, p.169	**Appropriate** Hospitalisation costs associated with the treatment of Grade 3+ AEs were sourced from the literature. Unit costs were derived from the NHS reference costs. The EAG checked the sources related to these costs and found them to be appropriate.

Source: EAG output
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; NHS = National Health Service; TA = technology appraisal; BNF = British National Formulary; eMIT = drugs and pharmaceutical electronic market information tool; NICE = The National Institute for Health and Care Excellence; PSSRU = Personal Social Services Research Unit AEs = adverse events; CEM cost-effectiveness model

4.2.7.1 Drug acquisition costs

The distribution of chemotherapy regimens was assumed to be the same for cemiplimab + chemotherapy and pembrolizumab + chemotherapy, with this information gathered the from EMPOWER-Lung 3 trial[1] and applied to both treatment arms in the CEM. The EAG note that the use of chemotherapy was more flexible in EMPOWER-Lung 3 than in KEYNOTE-189[34] and KEYNOTE-407.[35] In the CS, the company state that this assumption is necessary to ensure that any drug cost differences in the model are due to the cost of IOs rather than heterogeneity in chemotherapy use across the clinical studies, with clinical experts consulted by the company confirming that this is a reasonable assumption. Despite this, the EAG note that the distribution of chemotherapy regimes is still a matter of uncertainty. However, the EAG also note that minor differences in the distribution of chemotherapy regimes are unlikely to have a significant impact on the results in the CEM. The EAG also note that the prices for the treatments included in the submission in Appendix K[8] differ to those presented in the main CS and the CEM. The EAG have used the prices provided in the main CS and CEM in the EAG analyses.

4.2.7.2 Subsequent Treatment Costs

Following progression on first-line treatment, subsequent therapy costs were applied for patients in the post-progression health state. The distribution of post-progression subsequent treatment is shown in Table 4.13.

Table 4.13: Distribution of post-progression subsequent treatment

Initial (pre-progression) treatment		
Post-progression treatment	**Cemiplimab + chemotherapy**	**Pembrolizumab + chemotherapy**
Immunotherapies		
Pembrolizumab	0.6%	0.6%
Nivolumab	0.0%	0.0%
Atezolizumab	0.3%	0.3%
Chemotherapies		
Docetaxel	4.5%	4.5%
Carboplatin	5.4%	5.4%
Cisplatin	1.9%	1.9%
Gemcitabine	3.5%	3.5%
Paclitaxel	3.2%	3.2%
Pemetrexed	1.9%	1.9%
Total	**21.5%**	**21.5%**

Source: CS Document B, Table 55
Please note that due to rounding, there are minor disparities between sum of the individual immunotherapies and chemotherapies percentages and total percentage of post-progression subsequent treatments.

As noted by the company, in the EMPOWER-Lung 3 trial the uptake of subsequent therapies was lower than anticipated, likely due to the relatively short follow-up in post-progression in the trial at the data cut-off date, and therefore the same post-progression distribution of subsequent therapy

was assumed for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. The EAG note that this uptake of subsequent therapies is significantly lower than in other IO studies for patients with NSCLC. For example, in the five-year data from the KEYNOTE-189 trial, 55.3% of those in the pembrolizumab + chemotherapy treatment had subsequent pharmacological therapy, with 25.4% having subsequent anti-PD-L1 therapy. Furthermore, in the five-year data from the KEYNOTE-407 trial, 39.2% of those in the pembrolizumab + chemotherapy arm had subsequent pharmacological therapy, with 11.9% having subsequent anti-PD-L1 therapy. Any underestimation in subsequent treatment rates will lead to an underestimation of the costs associated with subsequent treatments.

A scenario analysis (Scenario 9) was conducted by the company where subsequent treatment distributions sourced from the EMPOWER-Lung 3 trial were reweighted to align with the overall distribution for IO and other systemic therapies observed in KEYNOTE-189. This scenario analysis showed that the results insensitive to this alternative subsequent treatment distributions, with the incremental costs changing from [redacted] in the base case to [redacted]. The EAG has conducted additional scenario analysis using alternative subsequent treatment distributions obtained from the KEYNOTE-189 and KEYNOTE-407 studies.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company presented an incremental cost-effectiveness analysis and cost comparison (which assumed equal efficacy for cemiplimab + chemotherapy and pembrolizumab + chemotherapy) with the list price for pembrolizumab and a patient access scheme (PAS) price for cemiplimab. These results are not appropriate for decision making because confidential prices are not yet available for pembrolizumab, chemotherapy treatments and immunotherapies included in the CEM.

The company's base-case deterministic cost-effectiveness results using the PAS discount for cemiplimab is shown in Table 1.1 and Table 5.2. Table 5.1 shows the deterministic analysis for the MHRA population with PD-L1 > 1% NSCLC that responded to treatment with cemiplimab + chemotherapy. The analysis compares cemiplimab + chemotherapy and pembrolizumab + chemotherapy for this population and shows cemiplimab + chemotherapy dominating pembrolizumab + chemotherapy by decreasing the cost by [redacted] per patient; and increasing total QALYs by [redacted]. The net monetary benefit of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy for a willingness to pay threshold of £20,000 was [redacted] (see Table 5.2).

Table 5.1: Company base-case deterministic results for cemiplimab + chemotherapy vs pembrolizumab + chemotherapy, using the PAS price of cemiplimab

Technology	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental Lys	Incremental QALYs	ICER (£)
Cemiplimab + Chemotherapy	[redacted]	3.26	[redacted]				
Pembrolizumab + Chemotherapy	£126,144	2.93	2.15	[redacted]	0.33	[redacted]	Dominating

Source: CS Document B, Section 3.9.1

Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; LYs = life years gained; PAS = Patient Access Scheme; QALY = quality-adjusted life year

Table 5.2: Net monetary benefit for company base-case deterministic results

Technology	Incremental costs (£)	Incremental QALY	ICER (£)	NMB at £20,000	NMB at £30,000
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Source: CS Model
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; NR = Not Reported

5.2 Company's sensitivity analyses

To explore uncertainty within their cost-effectiveness analysis, the company conducted a probabilistic sensitivity analysis over 1,000 iterations using the PAS price for cemiplimab. The company reported the following probabilistic sensitivity analysis (PSA) results showing cemiplimab + chemotherapy as the dominant intervention over pembrolizumab + chemotherapy and decreasing costs by [redacted] Table 5.3 and

Figure 5.1 show the probabilistic results reported by the company.

The EAG considers that the parametric distributions used to model uncertainty in the mean estimate were appropriate. The EAG verified that 1000 iterations for PSA in the model has low a sampling error.

Table 5.3: PSA results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy, using the PAS price of cemiplimab (company results)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER (£)
Cemiplimab + Chemotherapy	[redacted]	[redacted]			

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER (£)
Pembrolizumab + Chemotherapy	£126,224	2.16	[redacted]	[redacted]	Dominating

Source: CS Document B, Section B.3.8.1, Table 67

Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.1: ICEP for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy, using the PAS price of cemiplimab

Source: CS Document B, Section B.3.8.1, Figure 31
Abbreviations: GBP = pounds sterling; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; ICEP = Incremental Cost-Effectiveness Plane

The EAG re-ran the PSA analysis in the same model file and obtained similar results. In the EAG's run, cemiplimab + chemotherapy was dominant compared to pembrolizumab + chemotherapy, with incremental QALYs of [redacted] and incremental costs of [redacted] The results obtained by the EAG are reported in Table 5.4 and Figure 5.2.

Table 5.4: PSA results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy, using the PAS price of cemiplimab (EAG results)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER (£)
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	126,186	2.17	[redacted]	[redacted]	Dominating

Source: CS Model, EAG Analysis
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.2: EAG re-run of ICEP for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy, using the PAS price of cemiplimab

Source: CS model, EAG Analysis
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICEP = incremental cost-effectiveness plane; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY =quality-adjusted life year

The base-case one-way sensitivity analysis (OWSA) presented by the company included the deterministic analysis of disease progression and survival parameters of NSCLC patients. The EAG considered these parameters to be informative and relevant to the analysis. These results are shown in Table 5.5 and Figure 5.3.

Table 5.5: OWSA results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy

Parameter name	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Cemiplimab PFS	[redacted]	[redacted]	[redacted]
Pembrolizumab + Chemotherapy PFS	[redacted]	[redacted]	[redacted]
Cemiplimab OS	[redacted]	[redacted]	[redacted]
Pembrolizumab + Chemotherapy OS	[redacted]	[redacted]	[redacted]
Chemotherapy Curve PFS	[redacted]	[redacted]	[redacted]
Disease Management Cost - PD	[redacted]	[redacted]	[redacted]
Utility PD	[redacted]	[redacted]	[redacted]
Chemotherapy Curve OS	[redacted]	[redacted]	[redacted]
Disease Management Cost - PF	[redacted]	[redacted]	[redacted]
Utility PF	[redacted]	[redacted]	[redacted]

Source: CS Model
Abbreviations: CS = company submission; GBP = pounds sterling; ICER = incremental cost-effectiveness ratio; PFS = Progression-Free Survival; OS = Overall Survival; PD = Progressive Disease; PF = Progression Free; NMB = net monetary benefit; OWSA = one-way sensitivity analysis

Figure 5.3: OWSA results for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in net monetary benefit

Source: CS Model
Abbreviations: CS = company submission; GBP = pounds sterling; ICER = incremental cost-effectiveness ratio; PFS = Progression-Free Survival; OS = Overall Survival; PD = Progressive Disease; PF = Progression Free; NMB = net monetary benefit; OWSA = one-way sensitivity analysis

The OWSA suggested that cemiplimab PFS was the largest determinant of cost-effectiveness. Other important parameters included the pembrolizumab + chemotherapy PFS, OS of cemiplimab, OS of pembrolizumab + chemotherapy and health state costs of NSCLC.

The results from the company's deterministic scenario analysis are shown in Table 5.6. In all scenarios aside from two, cemiplimab + chemotherapy remained dominant over pembrolizumab + chemotherapy. In Scenario 10, where the company applied a hypothetical discount of 65% to the pembrolizumab list price in a CUA, the ICER was reported as [redacted]. In Scenario 11, where the company applied the same hypothetical discount to the cost comparison analysis, there was an assumption of equal QALYs, with pembrolizumab + chemotherapy found to be cost saving compared to cemiplimab + chemotherapy.

The subgroup analyses explored the cost-effectiveness of cemiplimab + chemotherapy for subgroups based on histology and PD-L1 levels. As shown in

5.3 Subgroup analyses

Table 5**.7**, cemiplimab + chemotherapy dominated pembrolizumab + chemotherapy in all the subgroups except for the squamous subgroup with PD-L1 values ≥50%. For this subgroup, cemiplimab + chemotherapy was less costly and was less effective compared to pembrolizumab + chemotherapy.

Table 5.6: Deterministic scenario analysis results for the company base-case

#	Model aspect	Base-case	Scenario analysis	Incremental costs Pembrolizumab + Chemotherapy (£)	Incremental QALYs Pembrolizumab + Chemotherapy	ICER versus Pembrolizumab + Chemotherapy (£)
	Company base-case	**N/A**	**N/A**	[redacted]	[redacted]	**Dominating**
1	Alternative PFS reference and two-step NMA	Log-logistic	Lognormal	[redacted]	[redacted]	Dominating
2	Alternative OS reference and two-step NMA	Log-logistic	Generalised gamma	[redacted]	[redacted]	Dominating
3	PFS constant HR NMA (log-logistic), no violation of PH assumption for PFS	2-Step NMA	Constant HR	[redacted]	[redacted]	Dominating
4	Applying HRs to PFS to estimate time on treatment	Equal to PFS	HR applies to PFS	[redacted]	[redacted]	Dominating
5	Waning of treatment effect applied to PFS/OS from 36 months	60 months	36 months	[redacted]	[redacted]	Dominating
6	Waning of treatment effect applied to PFS/OS from 36 to 60 months	60 months	36 months	[redacted]	[redacted]	Dominating
7	Continuation of treatment effect (no waning applied)	Treatment waning effect applied	Extrapolation of HR trend	[redacted]	[redacted]	Dominating

#	Model aspect	Base-case	Scenario analysis	Incremental costs Pembrolizumab + Chemotherapy (£)	Incremental QALYs Pembrolizumab + Chemotherapy	ICER versus Pembrolizumab + Chemotherapy (£)
8	Alternative health state utility values (NICE TA584 atezo+bev+chemo non-squamous IMpower 150 utilities using UK tariff)	EMPOWER LUNG 3 Trial, EORTC to EQ-5D-5L mapping	NICE TA584, Impower 150 utilities using UK tariff	[redacted]	[redacted]	Dominating
9	Subsequent treatment distribution	Subsequent treatment distribution from EMPOWER-LUNG 3 trial data	Alternative subsequent treatment distribution from KEYNOTE – 189 trial data	[redacted]	[redacted]	Dominating
10	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-utility analysis	Hypothetical discount applied to pembrolizumab list price: 0% in the cost-utility analysis	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-utility analysis	[redacted]	[redacted]	[redacted]
11	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-comparison analysis	Hypothetical discount applied to pembrolizumab list price: 0% in the cost-utility analysis the cost-utility analysis	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-comparison analysis	[redacted]	[redacted]	[redacted]
12	Alternative reference arm based on pooled KEYNOTE studies	EMPOWER Lung 3 Data	Pooled Keynote-189 and 407 data	[redacted]	[redacted]	Dominating

#	Model aspect	Base-case	Scenario analysis	Incremental costs Pembrolizumab + Chemotherapy (£)	Incremental QALYs Pembrolizumab + Chemotherapy	ICER versus Pembrolizumab + Chemotherapy (£)
	(log-logistic for PFS and OS)					
13	Exclude AE costs and disutilities	AE costs and disutilities included	AE costs and disutilities excluded	[redacted]	[redacted]	Dominating
14	Assume no drug wastage	Drug Wastage included	No drug wastage	[redacted]	[redacted]	Dominating
15	Cemiplimab + chemotherapy patients receive AUC5 carboplatin instead of AUC6	Cemiplimab + chemotherapy patients receive AUC6 carboplatin	Cemiplimab + chemotherapy patients receive AUC5 carboplatin	[redacted]	[redacted]	Dominating
16	75% of pembrolizumab + chemotherapy patients switch to pembrolizumab monotherapy Q6W after 4-months of treatment	pembrolizumab + chemotherapy – 11% of patients pembrolizumab monotherapy-89%	pembrolizumab + chemotherapy – 25% of patients pembrolizumab monotherapy-75%	[redacted]	[redacted]	Dominating
17	Include AE costs from KEYNOTE 189 and KEYNOTE 407 in the pembrolizumab + chemotherapy arm of the cost-comparison analysis	AE costs in the pembrolizumab + chemotherapy arm assumed equal to the EMPOWER-Lung 3 data in the cost-comparison analysis	Include AE costs from KEYNOTE 189 and KEYNOTE 407 in the pembrolizumab + chemotherapy arm of the cost-comparison analysis	[redacted]	[redacted]	Equal QALY

Source: CS Document B.3.8.3, EAG Analysis
Abbreviations: AE = adverse event; PFS = progression-free Survival, OS = Overall Survival; NMA = Network-Meta Analysis; ICER = incremental cost-effectiveness ratio; N/A = not applicable; QALY = quality adjusted life years; HR = hazard ratio; NICE = National Institute of Health and Care Excellence;

#	Model aspect	Base-case	Scenario analysis	Incremental costs Pembrolizumab + Chemotherapy (£)	Incremental QALYs Pembrolizumab + Chemotherapy	ICER versus Pembrolizumab + Chemotherapy (£)
TA = technology appraisal; AUC = area under the curve; AE = adverse event; Q6W = every 6 weeks; UK = Unites Kingdom; EORTC = European Organisation for Research and Treatment of Cancer						

5.4 Subgroup analyses

Table 5.7: Subgroup analysis results for the company base-case

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER (£)
Base case results (PD-L1 ≥1%, any histology)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£126,224	2.16	[redacted]	[redacted]	Dominating
PD-L1 1-49% squamous histology subgroup, assuming two-step NMA (exponential for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£100,943	1.52	[redacted]	[redacted]	Dominating
PD-L1 1-49% squamous histology subgroup, assuming constant HR NMA (exponential for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£100,948	1.53	[redacted]	[redacted]	Dominating
PD-L1 ≥50%, squamous histology subgroup, assuming two-step NMA (gamma for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£141,339	1.95	[redacted]	[redacted]	Less costs and less effective
PD-L1 ≥50%, squamous histology subgroup, assuming constant HR NMA (gamma for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£116,319	1.76	[redacted]	[redacted]	Less costs and less effective
PD-L1 1-49% non-squamous histology subgroup, assuming two-step NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£118,961	2.14	[redacted]	[redacted]	Dominating
PD-L1 1-49% non-squamous histology subgroup, assuming constant HR NMA (log-logistic for OS and log-logistic for PFS)					

Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£113,968	2.11	[redacted]	[redacted]	Dominating
PD-L1 ≥50%, non-squamous histology subgroup, assuming two-step NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£143,608	2.10	[redacted]	[redacted]	Dominating
PD-L1 ≥50%, non-squamous histology subgroup, assuming constant HR NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£130,765	1.70	[redacted]	[redacted]	Dominating

Source: CS Document B, Section B.3.8.4, Table 69
Abbreviations: CS = company submission; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; PFS = progression-free survival; PD-L1 = programmed death ligand 1; HR = hazard ratio; NMA = network meta-analysis; OS = overall survival

5.5 Model validation and face validity check

The company submitted model validation was conducted using the relevant items of the CADTH Model Validation Tool.[50]

5.5.1 Face validity assessment and technical verification

The EAG several minor errors in the initially submitted CEM, which were corrected by the company. The EAG were unable to replicate one scenario from the company scenario analyses in the subsequently submitted CEM; however, this issue was addressed by the company and EAG as part of the Factual Accuracy Check. The face validity and the technical verification of the model was found to be satisfactory by the EAG.

5.5.2 Comparisons with external data

In the survival analysis, the different parametric distributions were assessed for predictive accuracy with landmark survival estimates. For the chemotherapy PFS, the predictions from the different parametric models were compared with the two-year landmark PFS and median PFS from the EMPOWER-Lung 3 trial.[1]For the chemotherapy OS, the predictions from the different parametric distributions were compared with the five-year survival rates taken from several relevant previous studies, including four NICE submissions.[34-37,45,51] For the pembrolizumab + chemotherapy OS, the predictions from the different parametric distributions were also compared with the survival rates from several relevant previous studies, including NICE submission.[33-35,37]

As well as comparing the predictions to landmark survival estimates, the company also validated their preferred extrapolations for both PFS and OS with UK clinical expert lung oncologists at an advisory board and post-advisory board clarification questionnaire follow up.[5] As the same advisory board meeting, a number of other aspects of the CS were discussed and validated, including the treatment waning assumptions, adverse events, utilities and chemotherapy regimens.

6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Based on the considerations in the preceding sections of this EAG report, the EAG defined an EAG base-case. This EAG base-case included several adjustments to the company base-case presented in Section **Error! Reference source not found.**. These adjustments have been subdivided into three categories (derived from Kaltenthaler 2016):[52]

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG to derive the EAG base-case (using the CS base-case as starting point) are listed below.

Fixing errors

Some minor errors were identified by the EAG following the original submission of the CEM; however, these errors were corrected by the company prior to the PfCs.

Fixing violations

No violations to the NICE reference case were identified by the EAG.

Matters of judgement

Although there are questions surrounding the population eligible to receive cemiplimab + chemotherapy (Key Issue 1) and the comparators included in the company's decision problem not reflecting all of the treatments in the NICE scope (Key Issue 2), the EAG were unable to incorporate these issues into the EAG base case.

6.1.1.1 Equal ToT rates across treatment arms

In the company base case, the company assume that the ToT was equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. As stated in Section 4.2.4, the EAG note that by assuming that the assumptions that ToT is equal to PFS ignores the fact that ToT has an impact on PFS and OS in the clinical trials that provide the evidence, and that assuming that ToT is equal PFS will underestimate the costs for cemiplimab + chemotherapy and overestimate the costs for pembrolizumab + chemotherapy.

For consistency in the CEM, the estimates of ToT should either be estimated from the respective clinical trials or both effectiveness estimates and ToT should be assumed to be equal. As noted by the company, the EMPOWER-Lung 3 protocol allowed patients to continue treatment beyond disease progression under certain conditions, resulting in patients being treated beyond the 24-month stopping rule, and a HR or ToT relative to PFS of 1.17. The corresponding HR of ToT for pembrolizumab was 0.84, calculated from the

KEYNOTE-407[35] and KEYNOTE-189[34] trials and weighted by the split of squamous and non-squamous patients in EMPOWER-Lung 3[1]. Clinical advisors consulted by the company noted that the discrepancies in the ToT between the between cemiplimab + chemotherapy and pembrolizumab + chemotherapy treatment arms "*might be due to IO experience bias or reporting variations between trials"*. In the EAG base-case, the HRs of ToT estimated from EMPOWER-Lung 3 for cemiplimab + chemotherapy and KEYNOTE-407 and KEYNOTE-189 for pembrolizumab are used for consistency in the CEM. This aligns with Scenario 4 from the CS.

6.1.1.2 Assumption of a 'gradual' treatment waning beginning at 24 months

In the company base case, the company assumed that there was a continuation of the treatment effect from 24 months to 60 months, after which the estimated hazard of both disease progression and death is assumed to be equal to chemotherapy at five years for both PFS and OS. The EAG is concerned that the assumption of an 'immediate' waning effect after five years in the company base case is overestimating the treatment benefit of both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. As noted in Section 4.2.5, the EAG is of the opinion that applying a 'gradual' waning effect is more realistic than an 'immediate' waning at a specified time point.

In the EAG base, a gradual linear waning effect for both PFS and OS starting at 24 months (in line with the stopping rule for both cemiplimab and pembrolizumab) and ending at 60 months is used, after which the hazard of cemiplimab + chemotherapy and pembrolizumab + chemotherapy is assumed to be equal to the hazard for chemotherapy. It is worth noting that Scenario 5 from the CS applies a treatment effect to PFS/OS from 36 months. The scenario is replicated on the EAG base case as part of the EAG scenario analyses.

6.1.1.3 *Equal AE rates across treatment arms*

In the company base case, treatment-specific AE profiles are used, despite the chemotherapy backbone regime being assumed to be the same across treatments. The clinical expert consulted by the EAG noted that the Grade 3+ AEs included in the model would almost exclusively be caused by the chemotherapy regime rather than IO. As noted by the company, this results in a "misalignment" between the AEs and chemotherapy regime. Clinical expert advice gathered by the company stated that [redacted] and that there was [redacted].

In the EAG base, the AE profile for pembrolizumab + chemotherapy has been applied to both treatment arms. It is worth noting that Scenario 13 from the CS removes excludes AEs and their associated costs from the CEM. The scenario is replicated on the EAG base case as part of the EAG scenario analyses. The EAG has not included a scenario where AE rates are trial-specific and the chemotherapy backbone regime are trial-specific; that scenario would also be consistent. The results are not expected to be very different given the low cost of chemotherapy.

6.1.2 EAG exploratory scenario analyses

The EAG performed scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case. As well as replicating the company scenario analysis on

the EAG base case (**Error! Reference source not found.**) and the company sub-group analysis on the EAG base-case (**Error! Reference source not found.**), the EAG conducted some additional analyses (**Error! Reference source not found.**), detailed below.

- Additional Scenario 1 - Alternative subsequent therapy distributions based on KEYNOTE-407

In this additional scenario, the subsequent therapy distributions for both treatment arms were inflated to be in line with the subsequent therapies observed in the pembrolizumab + chemotherapy arm in the five-year outcomes from the KEYNOTE-407 trial. In this study, 39.2% of patients received any subsequent pharmacological therapy, with 11.9% of patients receiving any subsequent anti-PD(L)1 therapy. As shown in Table 6.1, the total immunotherapies were inflated to equal 11.9%, and the total chemotherapies were inflated to equal 27.3% (39.2% minus 11.9%). Once more, the proportions of immunotherapies and chemotherapies within these inflated totals were assumed to be equal to those from the EMPOWER-Lung 3 trial.

Table 6.1: Alternative post-progression treatment distributions

Post-progression treatment	Company Base Case	Company Scenario 9	EAG Additional Scenario 1	EAG Additional Scenario 2
Immunotherapies				
Pembrolizumab	0.6%	16.9%	7.9%	25.4%
Nivolumab	0.0%	0.0%	0.0%	0.0%
Atezolizumab	0.3%	8.5%	4.0%	0.0%
Immunotherapies Total	1.0%	25.4%	11.9%	25.4%
Chemotherapies				
Docetaxel	4.5%	6.5%	6.0%	6.5%
Carboplatin	5.4%	7.9%	7.3%	7.9%
Cisplatin	1.9%	2.8%	2.6%	2.8%
Gemcitabine	3.5%	5.1%	4.7%	5.1%
Paclitaxel	3.2%	4.7%	4.3%	4.7%
Pemetrexed	1.9%	2.8%	2.6%	2.8%
Chemotherapies Total	20.5%	29.9%	27.3%	29.9%
Immunotherapies + Chemotherapies Total	**21.5%**	**55.3%**	**39.2%**	**55.3%**

Source: CS Document B, Table 55
Abbreviations: EAG = Evidence Assessment Group
Please note that due to rounding, there are minor disparities between sum of the individual immunotherapies and chemotherapies percentages and total percentage of post-progression subsequent treatments.

- Additional Scenario 2 – Alternative subsequent therapy distributions based on KEYNOTE-189 with no atezolizumab

This additional scenario is identical to Company Scenario 9, with the exception that all patients prescribed subsequent immunotherapy are assumed to receive pembrolizumab, with no patients receiving atezolizumab. Clinical expert gathered by the EAG noted that in her experience atezolizumab is very rarely given in this population. Furthermore, as noted by the company, atezolizumab is only available for use in people with non-squamous disease and PD-L1 1-49% and has an 8% market share in that population.

- Additional Scenario 3 – Alternative approach to calculating subsequent therapy cost

In this additional scenario, the EAG calculated the subsequent treatment costs in a different way, by assuming 20% people who died, did so in the disease-free state and the cost of a full course of treatment is incurred for every patient who experiences disease progression. In the company base-case, it was calculated by assuming that the cost of subsequent treatment was distributed over time according to the percentage of the cohort in the progressive disease state in a given cycle. This percentage of the cohort is a cumulative percentage of the cohort in the progressive disease state over time, where the cycle person-time is a proportion of the total person-time across cycles. As an alternative approach, the EAG has assumed that a percentage of patients who died did so in the progression-free state. The full cost of the subsequent treatment course was incurred for every patient who experienced disease progression over relevant months following disease progression.

- Additional Scenario 4 - Alternative approach to calculating subsequent therapy cost

In this additional scenario, the subsequent treatment distribution from KEYNOTE-189 trial from Company Scenario 9 is applied with the EAG Additional Scenario 3 method of calculating the cost of subsequent treatment in a different way, to the EAG base-case.

- Additional Scenario 5 – Alternative approach to calculating subsequent therapy cost

This additional scenario is identical to EAG Additional Scenario 3, in which the EAG calculated the subsequent treatment costs in a different way but it was assumed that 5% of patients who died, did so in the disease-free state and the cost of a full course of treatment is incurred for every patient who experiences disease progression.

- Additional Scenario 6 – Alternative approach to calculating subsequent therapy cost

In this additional scenario, the subsequent treatment distribution from the KEYNOTE-189 trial from Company Scenario 9 is applied with the EAG Additional Scenario 5 method of calculating the cost of subsequent treatment in a different way, to the EAG base-case.

- Additional Scenario 7 - Generalized gamma distribution for PFS

In this additional scenario, the parametric distribution for PFS was changed to Generalized gamma. As described in Section 4.2.3, this distribution had the most accurate estimates of two-year PFS based on the landmark survival at two years for both cemiplimab +

chemotherapy (23.2%) and pembrolizumab + chemotherapy (25.0%) from the EMPOWER-Lung 3 trial and KEYNOTE-189 and KEYNOTE-407.

- Additional Scenario 8 - Gamma distribution for OS

In this additional scenario, the parametric distribution for OLS was changed to gamma. As described in Section 4.2.3, this distribution had the lowest AIC and second lowest BIC.

- Additional Scenario 9 - Generalized gamma distribution for PFS, gamma distribution for OS

This scenario is a combination of Additional Scenario 8 and Additional Scenario 9

- Additional Scenario 10 - Alternative utility values for PFS and Post-Progression from Nafees et al (2008)

In this additional scenario, the alternative utility values for PFS (0.673) and Post-Progression (0.473) from Nafees et al (2008)[43] were used. These utility values were discussed by the company in the CS, but not included in the company scenario analyses.

- Additional Scenario 11 - Alternative utility values for PFS and Post-Progression from Chouaid et al (2013)

In this additional scenario, the alternative utility values for PFS (0.710) and Post-Progression (0.670) from Chouaid et al (2013)[53] were used. These utility values were discussed by the company in the CS, but not included in the company scenario analyses.

6.1.3 EAG subgroup analyses

No additional subgroup analyses were conducted by the EAG.

6.2 Impact on the ICER of additional analyses undertaken by the EAG

6.2.1 The EAG base-case

The EAG base-case was presented in Section 6.1.1. Table 6.2 reports the individual impact of the changes proposed by the EAG to generate the EAG base-case results. Appendix 1 explains how the changes were implemented in the CEM.

Table 6.2: Deterministic and probabilistic EAG base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
CS base-case – Deterministic					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£126,144	2.15	[redacted]	[redacted]	Dominating
CS base-case – Probabilistic					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£126,224	2.16	[redacted]	[redacted]	Dominating
Matter of Judgement 1: Treatment Waning					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£125,857	2.10	[redacted]	[redacted]	Dominating
Matter of Judgement 2: Time on Treatment					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£116,751	2.15	[redacted]	[redacted]	Dominating
Matter of Judgement 3: Adverse Events same as Pembrolizumab + Chemotherapy					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£126,144	2.15	[redacted]	[redacted]	Dominating
EAG base-case (matters of judgment 1-3) – Deterministic					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£116,476	2.10	[redacted]	[redacted]	Dominating
EAG base-case (matters of judgment 1-3) – Probabilistic					
Cemiplimab + Chemotherapy	[redacted]	[redacted]			
Pembrolizumab + Chemotherapy	£116,595	2.11	[redacted]	[redacted]	Dominating

Source: EAG Analysis
Abbreviations: ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year
*All ICERs are for cemiplimab + chemotherapy

The change in assumptions regarding treatment waning had little impact on the costs, but had a significant impact on QALYs, changing the incremental QALYs from [redacted] in the company base-case to [redacted] in the EAG base-case. The change in assumptions regarding time on treatment had no impact on QALYs, but had a significant impact on costs, changing the incremental costs from [redacted] in the company base-case to [redacted] in the EAG base-case. The changes in assumptions regarding adverse events had little impact on either the costs or QALYs. In all cases, cemiplimab + chemotherapy remained the dominant strategy. These results are not appropriate for decision making, as a PAS price is used for cemiplimab only, with list prices for other immunotherapies and chemotherapies. Results using the confidential PAS prices for other immunotherapies and chemotherapies will be presented in the confidential PAS appendix.

6.2.2 Probabilistic sensitivity analysis

The estimated probabilistic results from the EAG base-case suggest that cemiplimab + chemotherapy dominates pembrolizumab + chemotherapy. Incremental QALYs for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy were [redacted] and incremental costs were [redacted] The probabilistic EAG base-case analyses indicated cost-effectiveness probabilities of [redacted] and [redacted] at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively.

The incremental cost-effectiveness plane showing the incremental costs and QALYs for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy is presented in **Error! Reference source not found.**. The cost-effectiveness acceptability curves for cemiplimab + chemotherapy and pembrolizumab + chemotherapy are presented in **Error! Reference source not found.**

[redacted]

Figure 6.1 Incremental cost-effectiveness plane (EAG base-case)

Source: EAG's base-case economic model
Abbreviations: QALY = Quality-adjusted life years

Figure 6.2 Cost-effectiveness acceptability curve (CEACs) (EAG base-case)

Source: EAG base-case economic model
Abbreviations: QALY = Quality-adjusted life years

6.2.3 One-way sensitivity analysis

The results from the one-way sensitivity analysis and its impact on the net monetary benefit in the EAG base-case are shown in Table 6.3 and displayed graphically in **Error! Reference source not found.**. The most influential parameters in the deterministic OWSA were pembrolizumab + chemotherapy PFS, chemotherapy curve PFS, cemiplimab PFS and cemiplimab OS.

Table 6.3: One-way sensitivity analysis on EAG base-case with net monetary values

Parameter name	Lower bound NMB (£)	Upper bound NMB (£)	Difference (£)
Cemiplimab PFS	[redacted]	[redacted]	[redacted]
Pembrolizumab + Chemotherapy PFS	[redacted]	[redacted]	[redacted]
Cemiplimab OS	[redacted]	[redacted]	[redacted]
Pembrolizumab + Chemotherapy OS	[redacted]	[redacted]	[redacted]
Chemotherapy curve PFS	[redacted]	[redacted]	[redacted]

Disease management cost - PD	[redacted]	[redacted]	[redacted]
Utility PD	[redacted]	[redacted]	[redacted]
Chemotherapy curve OS	[redacted]	[redacted]	[redacted]
Disease management cost - PF	[redacted]	[redacted]	[redacted]
Utility PF	[redacted]	[redacted]	[redacted]

Source: EAG base-case Model
Abbreviations: ICER = incremental cost-effectiveness ratio; PFS = Progression-Free Survival; OS = Overall Survival; PD = Progressive Disease; PF = Progression Free; NMB = net monetary benefit; OWSA = one-way sensitivity analysis

Figure 6.3 One-way sensitivity analysis with net monetary values

Source: EAG base-case economic model
Abbreviations: ICER = incremental cost-effectiveness ratio; PFS = Progression-Free Survival; OS = Overall Survival; PD = Progressive Disease; PF = Progression Free; NMB = net monetary benefit; OWSA = one-way sensitivity analysis

6.2.4 Company deterministic sensitivity analyses on the EAG base case

The results from the company deterministic sensitivity analysis and their impact on the cost-effectiveness results are shown in **Error! Reference source not found.**. The scenarios that impacted the incremental costs the most were scenarios 10 and 11, in which a discount in price is assumed for the pembrolizumab cost. The scenario that impacted the incremental

QALYs the most was scenario 7 where no treatment waning effect is assumed. The use of alternative health utility values in scenario 8 also had significant impact on the total QALY.

Table 6.4 Company deterministic scenario analyses on EAG base-case

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
	EAG base-case	**N/A**	[redacted]	[redacted]	**Dominating**
1	PFS reference and 2-step NMA (log-logistic)	Alternative PFS reference and 2-step NMA (log-normal)	[redacted]	[redacted]	Dominating
2	OS reference and two-step NMA (log-logistic)	Alternative OS reference and two-step NMA (generalised gamma)	[redacted]	[redacted]	Dominating
3	PFS 2-step NMA (log-logistic)	PFS constant HR NMA (log-logistic), no violation of PH assumption for PFS	[redacted]	[redacted]	Dominating
4	Applying the same HRs to PFS to estimate time on treatment	Applying different HRs to PFS to estimate time on treatment	[redacted]	[redacted]	Dominating
5	Waning of treatment effect applied to PFS/OS from 24 to 60 months	Waning of treatment effect applied to PFS/OS from 36 months	[redacted]	[redacted]	Dominating
6	Waning of treatment effect applied to PFS/OS from 24 to 60 months	Waning of treatment effect applied to PFS/OS from 36 to 60 months	[redacted]	[redacted]	Dominating
7	Waning of treatment effect applied to PFS/OS from 24 to 60 months	Continuation of treatment effect (no waning applied)	[redacted]	[redacted]	Dominating
8	Health state utility values (EMPOWER-Lung 3 trial,	Alternative health state utility values (NICE TA584 atezo+bev+chemo non-	[redacted]	[redacted]	Dominating

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
	EORTC to EQ-5D-5L mapping (UK tariff, modelled average)	squamous IMpower 150 utilities using UK tariff)			
9	Subsequent treatment distribution from EMPOWER-LUNG 3 trial data	Alternative subsequent treatment distribution from KEYNOTE – 189 trial data	[redacted]	[redacted]	Dominating
10	Discount applied to pembrolizumab list price is 0%	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-utility analysis	[redacted]	[redacted]	[redacted]
11	Discount applied to pembrolizumb list price is 0% in cost-utility analysis	Hypothetical discount applied to pembrolizumab list price: 65% in the cost-comparison analysis	[redacted]	[redacted]	Increased cost in cost-comparison analysis
12	Reference arm based on EMPOWER-Lung 3 data	Alternative reference arm based on pooled KEYNOTE studies (log-logistic for PFS and OS)	[redacted]	[redacted]	Dominating
13	AE costs and disutilities included	Exclude AE costs and disutilities	[redacted]	[redacted]	Dominating
14	Assume drug wastage	Assume no drug wastage	[redacted]	[redacted]	Dominating
15	Cemiplimab + chemotherapy patients receive AUC6 carboplatin	Cemiplimab + chemotherapy patients receive AUC5 carboplatin instead of AUC6	[redacted]	[redacted]	Dominating
16	pembrolizumab + chemotherapy – 11% of patients pembrolizumab monotherapy- 89%	75% of pembrolizumab + chemotherapy patients switch to pembrolizumab monotherapy Q6W after 4-months of treatment	[redacted]	[redacted]	Dominating

Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
17	AE costs in the pembrolizumab + chemotherapy arm assumed equal to the EMPOWER-Lung 3 data in the cost-comparison analysis	Include AE costs from KEYNOTE 189 and KEYNOTE 407 in the pembrolizumab + chemotherapy arm of the cost-comparison analysis (instead of assuming equal to EMPOWER-Lung 3)	[redacted]	[redacted]	Cost saving in a cost-comparison analysis.

Source: EAG base-case Model
Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year, AE = adverse events; PFS = progression-free survival; NMA = network meta-analysis; OS = overall survival; TA – technology appraisal; HR = hazard ratio; EORTC = The European Organisation for Research and Treatment of Cancer; AUC = area under the curve
*All ICERs are for cemiplimab + chemotherapy

6.2.5 EAG additional deterministic sensitivity analysis

The results from the additional deterministic sensitivity analysis conducted by the EAG on the EAG base-case are shown in Table 6.5. Appendix 1 explains how the changes needed to generate these scenarios were implemented in the CEM. As shown, all additional scenarios conducted by the EAG in relation to the subsequent treatments (Additional Scenarios 1-7) made very little difference to the incremental costs and incremental QALYs. As shown in Additional Scenario 9 and Additional Scenario 10, using a gamma distribution as the OS reference curve (for chemotherapy) in the survival analysis decreases the incremental QALYs substantially, from [redacted] in the EAG base-case to [redacted]. As shown in Additional Scenario 11, using the alternative utility values from Nafees et al 2008[43] decreases the incremental QALYs substantially; however, the EAG note that both the absolute values and decrement between these utility values can be considered extreme.

Table 6.5: EAG Additional Scenario Analyses on EAG base-case

Additional Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
	EAG base-case	**N/A**	[redacted]	[redacted]	**Dominating**
1	Subsequent therapy distributions based on EMPOWER-Lung 3	Alternative subsequent therapy distributions based on KEYNOTE-407	[redacted]	[redacted]	Dominating
2	Subsequent therapy distributions based on EMPOWER-Lung 3	Alternative subsequent therapy distributions based on KEYNOTE-189; pembrolizumab is assumed to the only immunotherapy used	[redacted]	[redacted]	Dominating
3	Cost of subsequent therapy is distributed over time as a percentage of the cumulative percentage of cohort in the progressive disease state over time	Alternative approach to calculating subsequent therapy cost, by assuming 20% people who died, did so in the disease-free state and the cost of a full course of treatment is incurred for every patient who experiences	[redacted]	[redacted]	Dominating

Additional Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
		disease progression			
4	Subsequent treatment distribution from EMPOWER LUNG-3 trial with cost of subsequent therapy distributed over time as a percentage of the cumulative percentage of cohort in the progressive disease state over time	Subsequent treatment distribution from KEYNOTE–189 trial with alternative approach to calculating subsequent therapy cost (20% people who died were in disease-free state)	[redacted]	[redacted]	Dominating
5	Cost of subsequent therapy is distributed over time as a percentage of the cumulative percentage of cohort in the progressive disease state over time	Alternative approach to calculating subsequent therapy cost, by assuming 5% people who died, did so in the disease-free state and the cost of a full course of treatment is incurred for every patient who experiences disease progression	[redacted]	[redacted]	Dominating
6	Subsequent treatment distribution from EMPOWER LUNG-3 trial with cost of subsequent therapy distributed over time as a percentage of the cumulative	Subsequent treatment distribution from KEYNOTE–189 trial with alternative approach to calculating subsequent therapy cost (5% people who died were in disease-free state)	[redacted]	[redacted]	Dominating

Additional Scenario #	EAG base-case input	Alternative input	Incremental costs (£)	Incremental QALYs	ICER* (£/QALY)
	percentage of cohort in the progressive disease state over time				
7	PFS reference and 2-step NMA (log-logistic)	PFS reference and 2-step NMA (Generalized gamma)	[redacted]	[redacted]	Dominating
8	OS reference and 2-step NMA (log-logistic)	OS reference and 2-step NMA (gamma)	[redacted]	[redacted]	Dominating
9	PFS and OS reference and 2-step NMA (log-logistic)	Generalized gamma distribution for PFS + gamma distribution for OS	[redacted]	[redacted]	Dominating
10	PFS/OS utilities from EMPOWER-Lung 3 trial, mapped from EORTC to EQ-5D-5L	Alternative utility values for PFS/OS from Nafees et al (2008)	[redacted]	[redacted]	Dominating
11	PFS/OS utilities from EMPOWER-Lung 3 trial, mapped from EORTC to EQ-5D-5L	Alternative utility values for PFS/OS from Chouaid et al. (2013), UK tariff (scenario in TA 584)	[redacted]	[redacted]	Dominating

Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; PFS = progression-free survival; OS = overall survival; EORTC = European Organisation for. Research and Treatment of Cancer
*All ICERs are for cemiplimab + chemotherapy

6.2.6 Sub-group analysis

The subgroup analysis was conducted on the EAG base-case and is given in Table 6.6. The results showed that cemiplimab + chemotherapy was dominant (less costly and more effective) than pembrolizumab + chemotherapy in all the subgroups except the squamous population. In the patients with squamous NSCLC with PD-L1 ≥ 50%, the intervention was less costly and less effective when compared to the comparator.

Table 6.6: Subgroup analysis on EAG base-case

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALY	ICER* (£)
Base case results (PD-L1 ≥1%, any histology)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	**-**	**-**	**-**
Pembrolizumab + Chemotherapy	**£116,476**	**2.10**	[redacted]	[redacted]	**Dominating**
PD-L1 1-49% squamous histology subgroup, assuming two-step NMA (exponential for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£90,412	1.45	[redacted]	[redacted]	Dominating
PD-L1 1-49% squamous histology subgroup, assuming constant HR NMA (exponential for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£90,815	1.46	[redacted]	[redacted]	Dominating
PD-L1 ≥50%, squamous histology subgroup, assuming two-step NMA (gamma for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£133,169	1.91	[redacted]	[redacted]	Less costly and less effective
PD-L1 ≥50%, squamous histology subgroup, assuming constant HR NMA (gamma for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£106,956	1.71	[redacted]	[redacted]	Less costly and less effective
PD-L1 1-49% non-squamous histology subgroup, assuming two-step NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£108,597	2.04	[redacted]	[redacted]	Dominating
PD-L1 1-49% non-squamous histology subgroup, assuming constant HR NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£103,416	1.97	[redacted]	[redacted]	Dominating

PD-L1 ≥50%, non-squamous histology subgroup, assuming two-step NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£143,901	2.10	[redacted]	[redacted]	Dominating
PD-L1 ≥50%, non-squamous histology subgroup, assuming constant HR NMA (log-logistic for OS and log-logistic for PFS)					
Cemiplimab + Chemotherapy	[redacted]	[redacted]	-	-	-
Pembrolizumab + Chemotherapy	£130,226	1.61	[redacted]	[redacted]	Dominating

Source: EAG base-case model
Abbreviations: EAG = Evidence Assessment Group, ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; PD-L1 = programmes death ligand 1; OS = overall survival; NMA = network meta-analysis; HR = hazard ratio; PFS = progression-free survival
*All ICERs are for cemiplimab + chemotherapy

6.3 Overall conclusions of the EAG's cost-effectiveness analysis

The estimated probabilistic results from the EAG base-case suggest that cemiplimab + chemotherapy dominates pembrolizumab + chemotherapy using the PAS price for cemiplimab and the list prices for other immunotherapies and chemotherapies. Incremental QALYs for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy were [redacted], and incremental costs were [redacted]. The probabilistic EAG base-case analyses indicated cost-effectiveness probabilities of [redacted] and [redacted] at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively.

Using the HRs of ToT estimated from the EMPOWER-Lung 3, KEYNOTE-407 and KEYNOTE-189 clinical trials in the EAG base-case rather than assuming ToT was equal to PFS had no impact on incremental QALYs, but had a significant impact on incremental costs, changing the incremental costs from [redacted] in the deterministic company base-case to [redacted] in the deterministic EAG base-case. Assuming a "gradual" treatment waning beginning at 24 months and ending at 60 months in the EAG base-case rather than a continuation of the treatment effect to 60 months followed by an "immediate" waning had little impact on the incremental costs, but had a significant impact on incremental QALYs, changing the incremental QALYs from [redacted] in the deterministic company base-case to [redacted] in the deterministic EAG base-case. The changes in assumptions regarding adverse events had little impact on either incremental costs or incremental QALYs.

The most influential parameters in the deterministic OWSA were pembrolizumab + chemotherapy PFS, chemotherapy curve PFS, cemiplimab PFS and cemiplimab OS. In the company deterministic scenario analyses, the scenarios that impacted the incremental costs the most were scenarios 10 and 11, in which a discount in price was assumed for the

pembrolizumab cost. The scenario that impacted the incremental QALYs the most was scenario 7, where no treatment waning effect is assumed.

From the EAG additional scenario analyses, the scenarios related to subsequent treatments made very little difference to the incremental costs and incremental QALYs. Using a gamma distribution as the OS reference curve (for chemotherapy) in the survival analysis decreased the incremental QALYs substantially, from [redacted] in the EAG base-case to [redacted]. Using the alternative utility values from Nafees et al 2008[43] decreases the incremental QALYs substantially.

The subgroup analysis showed that cemiplimab + chemotherapy was dominant in all subgroups except in patients with squamous NSCLC with PD-L1 ≥ 50%, in which cemiplimab + chemotherapy was less costly and less effective than pembrolizumab + chemotherapy.

Once more, it is worth emphasising these results are not appropriate for decision making as a PAS price is used for cemiplimab only, with list prices for other immunotherapies and chemotherapies. Results using the confidential PAS prices for other immunotherapies and chemotherapies will be presented in the confidential PAS appendix.

6.4 Overall conclusions of the EAG's critique

The company conducted three SLRs focusing on clinical effectiveness, cost effectiveness, and HRQoL respectively. The EAG judged the methods of the SLRs to be broadly appropriate, with the following caveats. The search strategy was well reported and thorough, although published filters had been edited before use. The EAG explored some issues around the eligibility criteria and concluded that there were no major concerns. To estimate the relative efficacy of cemiplimab the authors conducted a 2-step NMA, fitting parametric models for PFS and OS across all the arms of all the studies included in the NMA analyses, running the NMA analyses to estimate the scale and shape parameters for each outcome statistic and selecting the best fitting model. The results from the NMA indicated comparable effectiveness between cemiplimab + chemotherapy compared to pembrolizumab + chemotherapy overall, although with very wide credible intervals. The EAG noted greater uncertainty around the effectiveness of cemiplimab + chemotherapy in the PD-L1 1-49%, squamous sub-group for PFS as the estimate favoured pembrolizumab + chemotherapy in this population, again with wide credible intervals. The company stated that the relevant effect modifiers were not reported in the comparator studies at the relevant time points, in particular the % of patients receiving immunotherapy as a subsequent treatment, and consequently there is the potential for bias in the OS effectiveness estimate in favour of cemiplimab.

The company conducted a SLR with searches aimed at identifying cost-effectiveness studies, HRQoL and cost and resource use data to inform the economic model. These searches were considered fit for purpose; however, the EAG had some minor concerns regarding the HRQoL study type filter used by the company.

The EAG is concerned that the CS did not meet the NICE scope in two key areas. Firstly, the company included the PD-L1 ≥50%, squamous population despite the standard of care for this population sub-group being IO monotherapy. After querying this issue with the company in the PfCs and with the clinical advisor to the EAG, the EAG concludes that the PD-L1 ≥50%, squamous population sub-group is relevant as IO + chemotherapy would be the standard of care first line treatment for this population sub-group when urgent clinical intervention is needed (e.g., when the disease is progressing rapidly). Secondly, the company only included one comparator (pembrolizumab + chemotherapy) despite multiple treatments being included in the NICE scope. However, the EAG's clinical advisor agree that pembrolizumab + chemotherapy is the relevant comparator. The EAG has raised both points as key issues to highlight to the NICE committee that cemiplimab+ chemotherapy should only be administered to patients who would otherwise have received pembrolizumab + chemotherapy.

The first key issue the EAG raised regarding the economic analysis was the uncertainty in the assumptions regarding treatment discontinuation. The CEM assumed that the ToT was equal to PFS for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy, guided by an advisory board meeting where advisors were cautious about concluding discrepancies between the between cemiplimab + chemotherapy and pembrolizumab + chemotherapy treatment arms. The EAG was concerned that by assuming that ToT is equal PFS, this will underestimate the costs for cemiplimab + chemotherapy and overestimate the costs for pembrolizumab + chemotherapy. In the EAG base case, the hazard rates from EMPOWER-Lung 3 and KEYNOTE-407 are used to estimate time on treatment.

The second key issue the EAG raised regarding the economic analysis was the uncertainty in the treatment waning assumptions made in the CEM. In the CEM, the company have assumed that there is an "immediate" waning of the treatment effect for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy at 60 months. The EAG are concerned that applying waning on this "immediate" basis does not reflect the mechanism of action of Ios, lacks face validity and may be overestimating the treatment benefit of both cemiplimab and pembrolizumab. The EAG are of the opinion that a "gradual" waning of the treatment effect for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy may be more appropriate. In the EAG base case, a "gradual" treatment waning has been applied, beginning at 24 months (in line with the stopping rule for both treatment) and ending at 60 months.

The EAG had some concerns regarding the utility values used by the company for the PF and PD and the AE profiles used to incorporate AE disutilities in the CEM, however overall the approach to HRQoL in CS was considered fit for purpose.

The EAG had some concerns regarding the drug acquisition and subsequent treatment costs, however overall the approach taken to calculate costs and resource use in the CS was considered fit for purpose.

The company considered that this condition did not meet the disease severity modifier criteria.

The company base-case suggested that, after applying the PAS discount to the unit cost of cemiplimab, cemiplimab + chemotherapy was the dominant strategy over pembrolizumab + chemotherapy, increasing QALYs by [redacted] and decreasing costs by [redacted] in the probabilistic analysis, with a [redacted] probability of being cost-effective at a £20,000 threshold and a [redacted] probability of being cost-effective at a £30,000 threshold.

The EAG found no errors in the CEM after an initial revision by the company. The EAG base-case changed the assumptions regarding treatment waning to allow for a "gradual" rather than "immediate" waning, changed the assumptions for estimating time on treatment and equalised the adverse event profiles across the treatment arms. The EAG base-case suggested that, after applying the PAS discount to the unit cost of cemiplimab, cemiplimab + chemotherapy was the dominant strategy over pembrolizumab + chemotherapy by increasing QALYs by [redacted] and decreasing cost by [redacted], with a [redacted] probability of being cost-effective at a £20,000 threshold and a [redacted] probability of being cost-effective at a £30,000 threshold.

The choice of parametric survival model for OS, the assumption related to treatment discontinuation and the assumption related to treatment waning were found by the EAG to be the parameters with the largest impact on the cost-effectiveness results. Further structural scenarios were tested using scenario analyses proposed by the EAG and recreating scenarios from the CS on the EAG base-case, with cemiplimab + chemotherapy remaining dominant over pembrolizumab + chemotherapy the vast majority of scenarios when using the PAS price for cemiplimab. The significant uncertainties from the NMA mean that the cost-effectiveness analysis is also subject to substantial uncertainty.

The company subgroup analyses explored the cost-effectiveness of cemiplimab + chemotherapy for subgroups based on histology and PD-L1 levels. Results showed that cemiplimab + chemotherapy dominated pembrolizumab + chemotherapy in all the subgroups, with the exception of the squamous subgroup with PD-L1 values ≥50%. For this subgroup,

cemiplimab + chemotherapy was less costly and was less effective compared to pembrolizumab + chemotherapy. The EAG note that these subgroup analyses are subject to considerable uncertainty.

7 APPENDIX 1 - GENERATING THE EAG BASE-CASE AND EAG ADDITIONAL SCENARIO ANALYSIS

Generating the EAG's base-case analysis

The EAG's base-case model was built upon the company's base-case model. The changes made on the model are given below.

1. *Equal time on treatment rates across treatment arm*

In the 'Input_Efficacy TTD' sheet, change cells F7 and F9 from 'Equal to PFS' to 'HR applied to PFS'.

2. *Assumption of a 'gradual' treatment beginning at 24 months*

In the 'Input_Efficacy_OS' and 'Input_Efficacy_PFS' sheets, change cells F29 and F31 from '60' to '24'.

3. *Equal adverse event rates across treatment arm*

In 'Input_Safety_Tx' sheet, paste the array E12:E22 into array C12:C22.

Generating the EAG's additional scenario analyses

The EAG's additional scenario analyses was built upon the EAG base-case. The changes needed to generate the EAG's additional scenario analyses are given below.

1. *EAG Additional Scenario 1: Subsequent treatment distribution from the KEYNOTE – 407 trial applied to both the treatment arms:*

In the 'Input_Drug_Post_Prog' sheet, arrays C15:C17 and E15:E17 inflated by a factor of 11.9/SUM(C15:C17), and arrays C25:C30 and E25:E30 inflated by a factor of 27.3/SUM(C25:C30).

2. *EAG Additional Scenario 2: Subsequent treatment distribution from KEYNOTE – 189 trial applied to both the treatment arms, with pembrolizumab being the only alternative therapy immunotherapy considered.*

In the 'Input_Drug_Post_Prog' sheet, cells C15 and E15 changed to 25.4%, cells C17 and E17 changed to 0%, and arrays C25:C30 and E25:E30 inflated by a factor of 29.9/SUM(C25:C30).

3. *EAG Additional Scenario 3: Alternative approach to calculating the cost of subsequent therapy. Assume that 20% of the patients who die do so in the disease-free state, and that the cost of full course of treatment is incurred for every patient who experiences disease progression.*

a) In sheet 'Arm 1', a new column, AR was inserted. AR8 = 'Newly Progressive'. Input cell AR7 = 0.20, AR10 = 0. The cell AR12 =IF((AL10-AL11-(AM10-AM11)*$AR$7)<0,0,AL10-AL11-(AM10-AM11)*$AR$7) and extend the formula up to cell AR370. AR371 =SUM(AR10:AR370).
b) Input BP10 =(BP$2*BP$5*(1-BP$7)+BP$2*BP$6)*IF($A11<BP$3,0,1)*IF($A11<=BP$4,1,0) and extend up to BP369. Cell BP370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,BP10:BP369)/$AQ$371) and cell BP371 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,BP10:BP369)).
c) Input BR10 =(BR$2*BR$5*(1-BR$7)+BR$2*BR$6)*IF($A11<BR$3,0,1)*IF($A11<=BR$4,1,0) and extend up to BR369. Cell BR370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,BR10:BR369)/$AQ$371) and cell BR372 =(BR5+BR6)*BR2.
d) Input BY10 =(BY$2*BY$5*(1-BY$7)+BY$2*BY$6)*IF($A11<BY$3,0,1)*IF($A11<=BY$4,1,0) and extend up to BY369. Cell BY370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,BY10:BY369)/$AQ$371) and cell BY372 =(BY5+BY6)*BY2.
e) Input BZ10 =(BZ$2*BZ$5*(1-BZ$7)+BZ$2*BZ$6)*IF($A11<BZ$3,0,1)*IF($A11<=BZ$4,1,0) and extend it up to BZ369. Cell BZ370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,BZ10:BZ369)/$AQ$371) and cell BZ372 =(BZ5+BZ6)*BZ2.
f) Input CA10 =(CA$2*CA$5*(1-CA$7)+CA$2*CA$6)*IF($A11<CA$3,0,1)*IF($A11<=CA$4,1,0) and extend it up to CA369. Cell CA 370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,CA10:CA369)/$AQ$371) and cell CA372 =(CA5+CA6)*CA2.
g) Input CB =(CB$2*CB$5*(1-CB$7)+CB$2*CB$6)*IF($A11<CB$3,0,1)*IF($A11<=CB$4,1,0) and extend it to CB369. CellCB370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,CB10:CB369)/$AQ$371) and cell CB372 =(CB5+CB6)*CB2.
h) Input CC10 =(CC$2*CC$5*(1-CC$7)+CC$2*CC$6)*IF($A11<CC$3,0,1)*IF($A11<=CC$4,1,0), Cell CC370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,CC10:CC369)/$AQ$371) and cell CC372 =(CC5+CC6)*CC2
i) Input CD10 =(CD$2*CD$5*(1-CD$7)+CD$2*CD$6)*IF($A11<CD$3,0,1)*IF($A11<=CD$4,1,0) and extend it up to

CD369. Cell CD370 =IF($AQ$371=0,0,SUMIF($A$10:OFFSET($A$10,time_horiz*12,0),"<="&$AQ$371,CD10:CD369)/$AQ$371) and cell CD372 =(CD5+CD6)*CD2

j) Insert 4 new columns next to CT; CU, CV, CW, CX. CU8 = 'Alternative prog disease drug acquisition cost 8 months', CV8 = 'Alternative prog disease drug acquisition cost 4 month', CW8 = 'Alternative prog disease drug acquisition cost 1 months', CX8 = 'Alternative Total'.

k) Input CU10 =$AR10*SUM($BP$372,$BQ$372,$BR$372), CU11 =$AR11*SUM($BP$372,$BQ$372,$BR$372)+$AR10*SUM($BP$372,$BQ$372,$BR$372), CU12 =$AR12*SUM($BP$372,$BQ$372,$BR$372)+SUM($AR10:$AR11)*SUM($BP$372,$BQ$372,$BR$372) and extend this formula up to CU369.

l) Input CV10 =$AR10*SUM($BY$372,$BZ$372,$CA$372,$CB$372,$CC$372,$CD$372), CV11 =$AR11*SUM($BY$372,$BZ$372,$CA$372,$CB$372,$CC$372,$CD$372)+$AR10*SUM($BY$372,$BZ$372,$CA$372,$CB$372,$CC$372,$CD$372), CV12 =$AR12*SUM($BY$372,$BZ$372,$CA$372,$CB$372,$CC$372,$CD$372)+SUM($AR10:$AR11)*SUM($BY$372,$BZ$372,$CA$372,$CB$372,$CC$372,$CD$372) and extend this up to CV369

m) Input CW10 =$AR10*SUM(BS372,BT372,BU372,BV372,BW372,BX372,CE372,CF372,CG372,CH372,CI372,CJ372,CK372,CL372,CM372,CN372,CO372,CP372) and extend this up to CW369.

n) Input CX10 =SUM(CU10:CW10) and extend the formula up to CX369.

o) Input CY10 =CY9+(CX10*$H10*$C10) and extend it to CY369. Input CY370 =MAX(CY9:CY369)

p) The same changes were replicated in sheet 'Arm 3'.

4. *EAG Additional Scenario 4: Subsequent treatment distribution from KEYNOTE–189 trial with alternative approach to calculating subsequent therapy cost (20% of the patients who die do so in the disease-free state).*

   In this scenario, additional scenarios 1 and 4 are applied together to the EAG base case.

5. *EAG Additional Scenario 5: Alternative approach to calculating the cost of subsequent therapy. Assume that 5% of the patients who die do so in the disease-free state, and that the cost of full course of treatment is incurred for every patient who experiences disease progression.*

This scenario is identical to additional scenario 4, except that cell AR7 = 0.05.

6. *EAG Additional Scenario 6: Subsequent treatment distribution from KEYNOTE–189 trial with alternative approach to calculating subsequent therapy cost (5% of the patients who die do so in the disease-free state).*

In this scenario, additional scenarios 2 and 6 are applied together to the EAG base case.

7. *EAG Additional Scenario 7: Change PFS reference and 2-step NMA (Generalized gamma)*

In the ‘Input_Efficacy_PFS’ sheet, change cell B9 from ‘Log-logistic’ to ‘Generalised Gamma’.

8. *EAG Additional Scenario 8: Change OS reference and 2-step NMA (gamma)*

In sheet ‘Input_Efficacy_OS’, sheet, change cell B9 from ‘Log-logistic’ to ‘Gamma’.

9. *EAG Additional Scenario 9: Apply Generalized gamma distribution for ‘PFS Parametric distribution for reference curve’ and gamma distribution for ‘OS Parametric distribution for reference curve’.*

In the ‘Input_Efficacy_PFS’ sheet, change cell B9 from ‘Log-logistic’ to ‘Generalised Gamma’.

In sheet ‘Input_Efficacy_OS’, sheet, change cell B9 from ‘Log-logistic’ to ‘Gamma’.

10. *EAG Additional Scenario 10: Alternative utility values for PFS/OS from Nafees et al (2008).*

In the ‘Input_Efficacy’ sheet, change cell C6 from ‘EMPOWER Lung 3 trial, EORTC to EQ-5D-5L mapping (UK tariff, modelled average)’ to ‘Nafees et al (2008), UK tariff (scenario in TA584)’.

11. *EAG Additional Scenario 11: Alternative utility values for PFS/OS from Chouaid et al. (2013), UK tariff (scenario in TA 584)*

In the ‘Input_Efficacy’ sheet, change cell C6 from ‘EMPOWER Lung 3 trial, EORTC to EQ-5D-5L mapping (UK tariff, modelled average)’ to ‘Chouaid et al. (2013), UK tariff (scenario in TA584)’.

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Single Technology Appraisal

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

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

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 26 November** using the below comments table.

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

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 4, abbreviations list: The definition of ORR is incorrect	Please change *'Overall response rate'* to *'Objective response rate'*	To be consistent with the pre-specified endpoint/definition of ORR evaluated in EMPOWER-Lung 3	The EAG has made the suggested change.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12, first bulleted list: The text states that the technology is modelled to affect QALYs by *'Reducing the number of grade 3+ adverse events (AEs)'* This is potentially misleading as the both the EAG base case and the submitted cost-comparison analysis are	We suggest revising to *"Equalized adverse event (AE) rates were assumed in the EAG base case"* We also suggest adding the following text: *"An alternative cost-comparison base case presented by the company assumed equivalent clinical outcomes for cemiplimab and the relevant comparator"*	Currently the text is unclear and potentially misleading • how AEs/QALYs were modelled (and from who's perspective). • No that the company provided a cost comparison 'alternative base-case' assuming equivalent clinical effects (ie, only	No change – not a mistake or factual error.

modelled on equivalent safety. It is not clear whether these bullets describing how the technology is modelled to affect QALYs are from the company or EAG perspective		differences in treatment costs modelled)	

Issue 3

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 12, second bulleted list: Again, it is not clear which perspective this list is from. In addition, the first bullet is unclear and seems to relate to a scenario only from the company perspective	Please revise to make it clearer which perspective this text relates to (i.e. company or EAG)	Currently the text is unclear and potentially misleading	The EAG has clarified that this text related to the company economic model (CEM).

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12, second bulleted list ('technology is modelled to affect costs by'): The meaning of the second bullet in this list is unclear and does not make sense in combination with the first bullet	Please delete this bullet and add a separate sentence regarding considerations around the list vs PAS price for cemiplimab and comparator after the bulleted list	Currently the text is unclear and potentially misleading	The EAG has removed the second bullet point.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12, final bullet: *'Using alternative utility values previous used in NICE submissions in this clinical area decrease the incremental QALY gain for cemiplimab + chemotherapy'*	Please change *'previous'* to *'previously'*	Typographical error	The EAG has made the suggested change.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13, Table 1.2 *'Patients who are contra-indicated to IO + chemotherapy'* are stated as being *'ineligible for cemiplimab + chemotherapy*' in the same sentence This statement is unnecessary and confusing – by default a patient contra-indicated to a treatment is ineligible for it	Suggest deleting *'Patients who are contraindicated to IO + chemotherapy and'* so that the sentence only makes reference to patients with PD-L1 ≥50%	Currently the text is unclear and potentially misleading	Not a mistake or factual error. The text has been amended, with the intention of improving clarity: "*Patients with PD-L1 ≥50% in the squamous sub-group who do not require urgent clinical intervention, as well as patients from other subgroups who are contraindicated to IO + chemotherapy would therefore be ineligible for cemiplimab + chemotherapy."*

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, Table 1.4, row 3: *'roughly 41-42% had pembrolizumab crossover*	Please change *'KEYNOTE-187'* to *'KEYNOTE-189'*	Typographical error	The EAG has made the suggested change.

treatment following chemotherapy at 5 years in KEYNOTE-187 and KEYNOTE-407'			

Issue 8

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG Response**
Page 19, Table 1.9, row 6 (CS 10): The results for this scenario in the EAG report are incorrect	Please change the incremental costs for this scenario to [redacted], the incremental QALYs to [redacted] (as per the base case), and the ICER to [redacted].	Accuracy - Alignment with the CS.	The EAG has made the suggested change.

Issue 9

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG Response**
Page 19, Table 1.9, row 2 (CS 2): The incremental cost is given as [redacted]. According to the EAG CEM, this should be [redacted]	Please change [redacted] to [redacted]	Accuracy - Alignment with the EAG CEM	The EAG has made the suggested change.

(Also Page 96, Table 6.4, scenario 2)			

Issue 10

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 19, Table 1.9, row 5 (CS 8): The incremental cost is given as [redacted]. According to the EAG CEM, this should be [redacted] The incremental QALY is given as [redacted] (which is in fact the incremental LY). According to the EAG CEM, the incremental QALY should be [redacted] (Also Page 96, Table 6.4, Scenario 8)	Please change [redacted] to [redacted] Please change [redacted] to [redacted]	Accuracy - Alignment with the EAG CEM	The EAG has made the suggested change.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20, Table 1.9, row 2 (CS 11) *'Discount applied to pembrolizumb list price is 0% in cost-utility analysis'*	Please amend '*pembrolizumb' to 'pembrolizumab'*	Typographical error	The EAG has made the suggested change.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 29, Section 2.1 The text states that: *'The company responded that reasons why some patients are contraindicated to receive IO + chemotherapy include increased age, comorbidity burden and patient preference (i.e., avoiding side-effects)'* This is inaccurate. In our clarification responses, we	Please change *'contraindicated to receive'* to *'not selected to receive'*	Accuracy and alignment with the information provided at clarification	The EAG has made the suggested change.

described these as factors that are taken into account during individual patient risk:benefit assessment when deciding whether combination or monotherapy is a more appropriate treatment option/modality. We did not describe these factors as 'contraindicating' patients to combination treatment			

Issue 13

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 30, Section 2.3 The text describes participants in the EMPOWER-Lung 3 trial as having either Stage III or Stage IV disease. In fact, patients with locally advanced disease enrolled in the trial were required to have stage IIIB/C disease	Please change *'stage III'* to *'stage IIIB/C'* where appropriate throughout the document	Currently the text is unclear and potentially misleading	The EAG has made the suggested change.

(the study did not include patients with stage IIIA disease)			

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 34, Table 3.2, Row 1 (Intervention) & Row 2 (Comparator): Two of the chemotherapy regimens are incorrect: • *Paclitaxel 200mg/m2 IV plus carboplatin 75mg/m^2 IV on day 1 of every 21 days for 4 cycles* • *Pemetrexed 500 mg/m2 IV plus cisplatin AUC of 5 or 6 mg/ml/min IV on day 1 of every 21 days for 4 cycles*	Please amend to: • *Paclitaxel 200mg/m2 IV plus cisplatin 75mg/m^2 IV on day 1 of every 21 days for 4 cycles* • *Pemetrexed 500 mg/m2 IV plus carboplatin AUC of 5 or 6 mg/ml/min IV on day 1 of every 21 days for 4 cycles*	Typographical errors	The EAG has made the suggested change.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 36, Table Row 3 (Baseline characteristics): *'The company report that disease characteristics were well balanced between treatment groups at baseline, including for prognostic factors such as disease stage, performance status, and sex. However, it is unclear if this assessment was based on the ITT population or the MHRA label population. The balance of baseline characteristics in the MHRA label population does not appear to be as well balanced between the*	Please amend to reflect that the baseline characteristics were broadly well balanced between treatment groups in both the ITT and MHRA label population	Potentially misleading language that implies there were meaningful differences between the treatment groups in the MHRA label population	For balance, the EAG has amended the text to specify the proportions of people with specific characteristics (people aged ≥65 years and of females) that differed between trial arms. This replaces the text referring more generally to imbalances in baseline characteristics between groups.

cemiplimab + chemotherapy group and the placebo + chemotherapy group. Additionally, the EAG notes that amongst the subgroups there are some differences in baseline characteristics, particularly, age, sex, and brain metastasis which could act as treatment modifiers. There is also concern the trial population may not be representative of the UK patient population.' This is incorrect. The CS presents baseline characteristics for both the ITT and MHRA populations. At clarification, we described how the baseline characteristics in the MHRA population were generally well balanced between the two treatment			

arms in the MHRA label population, including with regards to factors such as sex and ECOG PS (≤ 5% difference between treatment arms). We also noted that the EPAR for cemiplimab + chemotherapy in NSCLC states that the baseline demographics and disease characteristics for the MHRA label population were *"equivalent to the ITT population"*.			

Issue 16

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 37, Table, Row 2 (Dropout rate): The drop out rate for other reasons in the cemiplimab + chemotherapy group is given as 17.6%. This should be 23.0% (i.e., 55/240 = 23%)	Please amend *'17.6%'* to *'23.0%'* Please add *'physician decision'* and *'sponsor decision'* to the list of other reasons for discontinuation	Correction of number error Accuracy/completeness	The EAG has made the suggested change to the percentage and added '*physician decision*' and '*other*' to reflect the information in Figure 37. '*Sponsor decision*' is not

The list of other reasons for discontinuation is incomplete			listed in Figure 37 therefore this has not been added.

Issue 17

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 38, Table, Row 1 (Results: efficacy outcomes': *'Pain symptoms at data cut-off compared to baseline were between the intervention group and placebo group were -4.31 (95% CI: -8.07, -0.55) in favour of the intervention (P = 0.0248)'* Sentence does not make sense	Please amend to: *'Pain symptoms at data cut-of compared to baseline were -4.31 (95% CI: -8.07, -0.55) in favour of the intervention (P = 0.0248)'*	To improve accuracy and readability of the document	The EAG has made the suggested change.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 38, Table, Row 1 (Results: efficacy outcomes': *'However, there were uncertainties regarding differences in HRQoL outcomes between intervention and comparator group*' We feel that general reference to 'uncertainties' is not a true reflection of the HRQoL data. As described on pages 55 to 57 of the CS, there was a delay in time to clinically meaningful deterioration favouring cemiplimab + chemotherapy for several function and symptom domains on the QLQ-C30 and QLQ-LC13. Some of these results were statistically significant.	Suggest that the text is amended to be more specific about the uncertainties the EAG is referring to. We also suggest that information on time to definitive clinically meaningful deterioration is added for balance	To accurately reflect the HRQoL data presented in the CS	Text amended in table 3.2 and section 3.2.4.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 39, Table, Row 2 (Results: subgroup analyses): The incorrect abbreviation is given for objective response rate (OR instead of ORR)	Please amend *'OR'* to *'ORR'*	Accuracy	The EAG has made the suggested change.

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 40, Section 3.2.1: *'In the EMPOWER-Lung 3 trial, [redacted] of the participants assigned to a carboplatin chemotherapy regimen received AUC 6 carboplatin dose, and [redacted] received an AUC 5 carboplatin dose'* It is not clear from this text these numbers refer to to	Please amend to: *'In the cemiplimab + chemotherapy arm of EMPOWER-Lung 3, [redacted] of the participants were selected by investigators at baseline to receive an AUC 6 carboplatin dose, and [redacted] were selected to receive an AUC 5 carboplatin dose'*	To improve accuracy	The EAG has made the suggested change.

the cemiplimab + chemotherapy arm of the trial and reflect clinician's decision at baseline as recorded on the CRF to use AUC5 or AUC6 carboplatin.			

Issue 21

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 41, Section 3.2.3: *'The company report that other than pain symptoms, there were no notable differences between cemiplimab + chemotherapy group and placebo + chemotherapy group in any of the EORTC patient QLQ-C30 HRQoL domains'* By only describing the results for change from baseline, the EAG are not giving an accurate representation of the	Please add in details of the time to clinically meaningful deterioration for balance	To accurately reflect the HRQoL data presented in the CS	The EAG has made the suggested change.

overall HRQoL data.. As described on pages 55 to 57 of the CS, there was a delay in time to clinically meaningful deterioration favouring cemiplimab + chemotherapy for several function and symptom domains on the QLQ-C30 and QLQ-LC13. Some of these results were statistically significant.			

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 42, Section 3.2.5: [redacted] *patients in the EMPOWER-lung 3 study received an AUC 5 carboplatin dose which is not routinely given amongst this patient population in the UK currently'* It is not clear from this text that this just related to the	Please amend to: [redacted] *patients in the cemiplimab + chemotherapy arm of EMPOWER-lung 3 study were selected by investigators at baseline to initiate treatment with an AUC 5 carboplatin dose which is not routinely possible for patients with squamous disease in the UK currently as NHS commissioning policy (Blueteq protocol) mandates that patients are*	To improve accuracy	The EAG has made the suggested change.

cemiplimab + chemotherapy arm of the trial and that initiation with AUC6 carboplatin is only mandated for patients with squamous disease.	*'fit' to initiate treatment with AUC 6 carboplatin'*		

Issue 23

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 43, Table 3.3, Row 1 (Statistical methods): *'The difference in the shape and scale parameters of this parametric model for the from the shape and scale parameters of the reference treatment (chemotherapy) were estimated using a fixed effect bivariate normal NMA'* This sentence does not flow well	*Please delete 'for the'*	Typographical error	The EAG has made the suggested change.

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 46, Table 3.4, Row 2: *'KENOTE-024'*	Please amend to 'KEYNOTE-024	Typographical error	The EAG has made the suggested change.

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 48, Section 3.3.3: *'However, 41-42% had received pembrolizumab in study crossover at 5 years in the KEYNOTE-187 and KEYNOTE-407 studies'* The study number is incorrect; it should be KEYNOTE-189	Please amend *'KEYNOTE-187'* to *'KEYNOTE-189'*	Typographical error	The EAG has made the suggested change.

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49, Section 3.3.4.2, Paragraph 2: This paragraph only mentions PFS results for the PD-L1 1-49% squamous group, stating that results favoured pembrolizumab + chemotherapy. For balance, the OS results should also be described. While there was no statistically significant difference, the point estimate favoured cemiplimab + chemotherapy in the time-varying NMA at all time points.	Please add in the OS results for the PD-L1 1-49% squamous group	To avoid the misleading impression that survival outcome treatment effect estimates from the NMA consistently favoured pembrolizumab + chemotherapy in this subgroup.	OS results for PDL 1-49% squamous subgroup added.

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49, Section 3.3.4.2, Paragraph 2: *'This effect estimate is in the opposite direction to the base-case (PD-L1 ≥1%) PFS (HR 1.01, 95% CrI 0.72 to 1.42); however, there is overlap in 95% CrIs between the base-case (PD-L1 ≥1%) and PD-L1 1-49% squamous group'.* This is incorrect: the effect estimate is in the same direction as the base case	Please remove this text	To improve accuracy	The EAG has edited the text: *"This effect estimate is more favourable to pembrolizumab + chemotherapy than found for the base-case (PD-L1 ≥1%) PFS (HR 1.01, 95% CrI 0.72 to 1.42)"*

Issue 28

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 50, Section 3.4, Paragraph 2:	Please amend to: *'Also, 43 studies were excluded from the SLR as no results had yet been published;*	Potentially misleading language that implies the	As the company have pointed out that the 43 studies were excluded as results had yet been

'*Also, 43 studies were excluded from the SLR due to missing information*; *however, there was no indication that the systematic review team attempted to contact authors for these data'* This is incorrect. Results for these 43 trials had not been published at the time of the SLR. They were removed from the evidence base, but flagged as being relevant once data become available	*however, they were flagged as being potentially relevant once data become available'*	data were published but key information was missing	published, the EAG has removed this as an issue from the conclusions section.

Issue 29

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 50, Section 3.4, Paragraph 3: *'Additionally, baseline imbalances were identified by the EAG between the cemiplimab +*	Please remove this text	Potentially misleading language that implies there were meaningful differences between the treatment groups in the MHRA label population	The EAG has made the suggested change.

chemotherapy group and placebo + chemotherapy groups for the MHRA label (PD-L1, 1-100%) population in relation to age, sex, and brain metastasis, which could act as treatment modifiers' We do not agree that there are imbalances between the treatment groups in sex or presence of brain metastases (≤ 5% difference between treatment arms), or in age (1 year difference in mean age between the treatment arms; ~7% difference in the % of patients aged 65 years or over)			

Issue 30

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 51, Paragraph 2: *'The EAG noted uncertainty around the effectiveness of cemiplimab + chemotherapy in the PD-L1 1-49%, squamous sub-group as the data indicated that pembrolizumab + chemotherapy may be more effective in this population'* This is misleading. All OS and PFS results in this subgroup analysis were comparable between cemiplimab + chemotherapy vs pembrolizumab + chemotherapy across all time points in the time varying HR NMAs and in the constant HR NMA.	Please delete this statement	Potentially misleading language that implies survival outcome treatment effect estimates from the NMA consistently favoured pembrolizumab + chemotherapy in this subgroup.	The EAG has added "for PFS" for clarification. The EAG disagrees that the company's NMA shows the two treatments are comparable. In the EAG's view, the CrIs are too wide to draw that conclusion.

Issue 31

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 53, Table Row 2 (Data sources for model input Cross reference to CS is missing	Please add *'Appendix G, Appendix H, Appendix I'*	For completeness	The EAG has made the suggested change.

Issue 32

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 53, Table Row 3 (Eligibility criteria for inclusion of economic evaluations: Cross reference to CS is missing	Please add *'Appendix G, 1.1, Table 95'*	For completeness	The EAG has made the suggested change.

Issue 33

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 53, Table Row 4 (Eligibility criteria for inclusion of health state utility value studies: Cross reference to CS is missing	Please add *'Appendix H, 1.1, Table 98'*	For completeness	The EAG has made the suggested change.

Issue 34

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 53, Table Row 5 (Eligibility criteria for inclusion of resource use and cost studies: Cross reference to CS is missing	Please add *'Appendix G, 1.1, Table 95'*	For completeness	The EAG has made the suggested change.

Issue 35

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 60, Table, Row 4 (Treatment waning assumption) The incorrect page number is given for the relevant section in the CS	Please amend *'p.162'* to *'p.131'*	Typographical error	The EAG has made the suggested change.

Issue 36

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 61, Section 4.2.3: *'The PFS and OS survival curves were estimated using a 2-part NMA*' This is incorrect, it was a 2-step NMA	Please amend *'2-part NMA'* to *'2-step NMA'*	To improve accuracy	The EAG has made the suggested change.

Issue 37

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 64, Table 4.5, Column 2 (NMA model) Several of the descriptions in this column are incorrect (appear to have been copied from the corresponding PFS table)	Please amend as follows: Exponential: amend to *'Excluded due to PH violations'* Gompertz: amend to *'Favoured (second lowest AIC)'* Log-normal: amend to *'Deprioritized'*	For accuracy and consistency with the CS	The EAG has made the suggested changes.

Issue 38

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 64, Table 4.5, Column 5 (Total AIC across NMA) The figures in this column are incorrect (appear to have been copied from the corresponding PFS table)	Please amend as follows: Exponential: *'6,995.24'* Weibull: *'6,951.62'* Gompertz: *'6,928.61'* Log-normal: *'6,958.01'* Log-logistic: *'6,925.18'* Gamma: *'6,957.13'*	For accuracy and consistency with the CS	The EAG has made the suggested changes.

	Generalised gamma (fixed Q): *'6,933.79'*		

Issue 39

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 64, Table 4.5, Column 6 (Chemo reference) The figures in this column are incorrect	Please amend as follows: Exponential: *'3.7%'* Weibull: *'1.8%'* Gompertz: *'0.8%'* Log-normal: *'9.4%'* Log-logistic: *'8.4%'* Gamma: *'2.2%'* Generalised gamma (fixed Q): *'5.3%'*	For accuracy and consistency with the CS	The EAG has made the suggested changes.

Issue 40

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 64, Table 4.5, Column 7 (Cemi + chemo) The figures in this column are incorrect	Please amend as follows: Exponential: '*17.2%'* Weibull: '*11.9%'*	For accuracy and consistency with the CS	The EAG has made the suggested changes.

	Gompertz: *'5.7%'* Log-normal: '*25.0%'* Log-logistic: '*21.5%'* Gamma: '*13.6%'* Generalised gamma (fixed Q): '*19.5%'*		

Issue 41

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 64, Table 4.5, Column 8 (Pembro + chemo) The figures in this column are incorrect	Please amend as follows: Exponential: '*11.9%'* Weibull: '*6.5%'* Gompertz: *'3.4%'* Log-normal: '*19.8%'* Log-logistic: '*17.6%'* Gamma: '*9.2%'* Generalised gamma (fixed Q): '*14.6%'*	For accuracy and consistency with the CS	The EAG has made the suggested changes.

Issue 42

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 65, Paragraph 1: *'It also had the lowest total AIC and total AIC across all trial arms'* *Repetition of 'total AIC'*	Please amend to: *'It also had the lowest total AIC across all trial arms'*	Typographical error	The EAG has amended the typographical error so it now reads: *"It also had the lowest total AIC and total BIC across all trial arms".*

Issue 43

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 66, Table 4.6, Row 2: *'Pembrtolizumab + chemotherapy'*	Please amend to *'Pembrolizumab + chemotherapy'*	Typographical error	The EAG has made the suggested changes.

Issue 44

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 73, Table 4.13:	Please amend *'21.5%'* to *'21.3%'*	Typographical error	This difference is due to rounding. The EAG has now

In both columns, the %s add up to 21.3%, not 21.5%			included a footnote indicating this.

Issue 45

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 75 *'The net monetary benefit of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy for a willingness to pay threshold of £20,000 was* [redacted] *(see* ***Error! R eference source not found.****)*' Table 5.2 gives the NMB at £20,000 as [redacted]	Please amend the value in the text to [redacted]	For accuracy and consistency with the company CEM	The EAG has made the suggested changes.

Issue 46

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 75, Table 5.1: There should be a minus sign on the incremental cost The footnote gives that source as Section 3.9.1. of the CS; this should be Section 3.7.1	Please add a minus sign to the incremental cost in Table 5.1 Please change '3.9.1' to '3.7.1'	For accuracy Typographical error	The EAG has made the suggested changes.

Issue 47

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 75, Table 5.2: The incremental QALY does not require a £ sign	Please remove the £ sign from the incremental QALY	Typographical error	The EAG has made the suggested changes.

Issue 48

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 76, Section 5.2, Paragraph 1: *'The company reported the following probabilistic sensitivity analysis (PSA) results showing cemiplimab + chemotherapy as the dominant intervention over pembrolizumab + chemotherapy and decreasing costs by* [redacted] This text reports the deterministic incremental cost, not the probabilistic result.	Please change [redacted] to [redacted]	For accuracy and consistency with the company CEM	The EAG has made the suggested changes.

Issue 49

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 80, Table 5.6, and preceding text on Page 79: There is a lack of clarity in the text and table regarding which scenarios the EAG have retained and which they have altered, so we are unclear whether we should be checking scenarios against the original CS model or the EAG model. If the table is wholly based on the original CS, then several of the incremental costs and incremental QALYs are incorrect	Please reword the text on Page 79 for clarity and make clearer in Table 5.6 which scenarios have been retained/altered	Currently the text is unclear and potentially misleading	The EAG has corrected Table 5.6 and edited the text in this section.

Issue 50

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>Page 80, Table 5.6 and preceding text on Page 79

Scenario 9, exploring the changing of the subsequent treatment distribution, still results in lower costs for cemiplimab + chemotherapy versus the comparator. However, the text on Page 79 indicates “changing the subsequent treatment distribution had the potential to make cemiplimab + chemotherapy more costly when compared to</td>
<td>It is understood that the distributions used to run Scenario 9 were not available in the CS, and following further review, additional errors were identified for this Scenario in the CS (e.g. values in CS did not reflect the current cemiplimab PAS price per the base-case).

As such, the Company proposes to update the wording and table figures to reflect the scenario using the following subsequent treatment distributions, calculated from KEYNOTE-189:

Alternative distribution of post-progression subsequent treatment for interventions administered in PD-L1 ≥1%, informed by KEYNOTE-189 study
<table>
<tr><th rowspan="2">Post-progression treatment[a] ↓</th><th colspan="2">Pre-progression treatment, post-progression distributions from EMPOWER-Lung 3 aligned to KEYNOTE-189 study[b]</th></tr>
<tr><th>Cemiplimab combination</th><th>Pembrolizumab + chemotherapy[c]</th></tr>
<tr><td>Immunotherapy</td><td>25.4%</td><td>25.4%</td></tr>
<tr><td>Pembrolizumab</td><td>16.9%</td><td>16.9%</td></tr>
<tr><td>Nivolumab[d]</td><td>0.0%</td><td>0.0%</td></tr>
<tr><td>Atezolizumab</td><td>8.5%</td><td>8.5%</td></tr>
<tr><td>Chemotherapy</td><td>30.0%</td><td>30.0%</td></tr>
<tr><td>Docetaxel</td><td>6.5%</td><td>6.5%</td></tr>
<tr><td>Carboplatin</td><td>7.9%</td><td>7.9%</td></tr>
<tr><td>Cisplatin</td><td>2.8%</td><td>2.8%</td></tr>
<tr><td>Gemcitabine</td><td>5.1%</td><td>5.1%</td></tr>
</table>
</td>
<td>Accuracy of results due to errors in CS, and inaccurate summary of Table 5.6 results</td>
<td>The EAG has heavily edited this section, including updating Scenario 9 in Table 5.6 and removing the text referring to the previous Scenario 9.

Given the changes to Company Scenario 9 following the inaccuracies identified by the company in the CS, the EAG have also now removed Key Issue 6 (related</td>
</tr>
</table>

pembrolizumab + chemotherapy".

Inaccuracies have also been identified in the CS meaning values for Scenario 9 in the CS and the EAG report are inaccurate.

Paclitaxel	4.7%	4.7%
Pemetrexed	2.8%	2.8%
Total	**55.3%**	**55.3%**

Notes: *a) Subsequent therapies received by ≥1% of patients in either the cemiplimab combination or chemotherapy arm of the EMPOWER-Lung 3 trial were included in the model; b) Subsequent treatment distributions in the model (sourced from EMPOWER-Lung 3) were reweighted to align with the overall distribution for immunotherapy and other systemic therapies observed in KEYNOTE-189 study (Garassino et al. 2023) c) assumed same as cemiplimab combination*

CS: Table 1: Results of scenario analyses, PD-L1 ≥1% and any histology

Scenario 9: Alternative subsequent treatment distribution							
Cemiplimab + chemo	[redacted]	3.26	[redacted]	-	-	-	-
Pembro + chemo	137,939	2.93	2.15	[redacted]	0.33	[redacted]	Dominant

Following the provision of the full detail of this scenario, it is proposed that the sentence referring to the subsequent treatment scenario is removed.

In addition to this, Scenario 9 in Table 5.6 of the EAG report should be updated to account for the corrected values of the scenario (above):

Table Error! No text of specified style in document.**.2: Deterministic scenario analysis results for the company base-case**

#	Model aspect	Base-case	Scenario analysis	Incremental costs Pembrolizumab + Chemotherapy (£)	Incremental QALYs Pembrolizumab + Chemotherapy	ICER versus Pembrolizumab + Chemotherapy (£)

to subsequent treatments).

Given the removal of Key Issue 6, a number of textual changes and changes to tables have been made throughout the EAG report.

	9	Subsequent treatment distribution	Subsequent treatment distribution from EMPOWER-LUNG 3 trial data	Alternative subsequent treatment distribution from KEYNOTE – 189 trial data	[redacted]	[redacted]	Dominating		

Issue 51

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 80, Table 5.6 In scenario 7, 'Extrapolation of HR trend does not need to be underlined'	Please remove underlining	Typographical error	The EAG has made the suggested changes.

Issue 52

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 81, Table 5.6 For scenario 10, the ICER is stated to be 'Dominating'	Please change the ICER to [redacted]	Accuracy	The EAG has made the suggested changes.

This is incorrect/inconsistent with the CS			

Issue 53

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 81, Table 5.6 For scenario 11, the ICER is stated to be £[redacted] This is incorrect/inconsistent with the CS	Please change to 'Equal QALYs' per the cost-comparison analysis the scenario relates to and for consistency with the CS (Table 68)	Accuracy	The EAG has made the suggested changes.

Issue 54

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 97, Table 5.7 The table reports the probabilistic base case results instead of the deterministic base case results	Please change the values under *'Base case results (PD-L1 ≥1%, any histology)'* to reflect the deterministic results	Accuracy	The EAG has made the suggested changes. These changes are on Page 84 rather than on Page 97 as indicated by the company.

Issue 55

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 89, Table 6.1: The *'Immunotherapies + chemotherapies total'* is incorrect. It should be 21.3%, not 21.5% We also note that the %s do not add up in other columns in this table, but is unclear whether these are due to rounding	Please amend *'21.5%'* to *'21.3%'* Please check all other total %s and if necessary clarify in a footnote if they do not add up due to rounding	Typographical error Clarity	This difference is due to rounding. The EAG has now included a footnote indicating this.

Issue 56

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 89-90, Additional scenarios These scenarios are unrealistic/uninformative as patients are not routinely offered retreatment with IO in UK clinical practice after	Please remove unrealistic/uninformative scenario analyses	These scenarios are unrealistic/ uninformative as they do not reflect current UK clinical practice	No change – not a mistake or factual error.

receiving IO in a previous line of therapy.			

Issue 57

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 96, Table 6.4, Row 3 The incremental cost given for scenario 2 is inconsistent with the EAG model	Please change [redacted] to [redacted]	Accuracy and consistency with EAG CEM	The EAG has made the suggested changes.

Issue 58

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 96, Table 6.4, Row 9 The incremental costs and incremental QALY given for scenario 8 is inconsistent with the EAG model	Please change [redacted] to [redacted] Please change [redacted] to [redacted]	Accuracy and consistency with EAG CEM	The EAG has made the suggested changes.

Issue 59

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 97, Table, Row 6 The incremental costs given for scenario 12 is inconsistent with the EAG model	Please change [redacted] to [redacted]	Accuracy and consistency with EAG CEM	The EAG has made the suggested changes.

Issue 60

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 105, Section 6.4, Paragraph 1: *'One study was excluded by the company that may have satisfied the eligibility criteria*' There is no previous mention of this in the relevant sections of the EAG report. We are unaware of any excluded	Please clarify which SLR this relates to and how the study may have satisfied the eligibility criteria	Clarity	This issue has now removed from the EAG report as the study is not considered to have met the eligibility criteria for the effectiveness SLR.

studies that may have met the eligibility criteria.			

Issue 61

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 105, Section 6.4, Paragraph 2: *'…however, the data indicated that pembrolizumab + chemotherapy may be more effective in the PD-L1 1-49/%, squamous sub-group*' This is misleading. All OS and PFS results in this subgroup analysis were comparable between cemiplimab + chemotherapy vs pembrolizumab + chemotherapy across all time points in the time varying HR NMAs and in the constant HR NMA.	Please delete this text	Potentially misleading language that implies survival outcome treatment effect estimates from the NMA consistently favoured pembrolizumab + chemotherapy in this subgroup.	The EAG has added "for PFS" for clarification. The EAG disagrees that the company's NMA shows the two treatments are comparable. In the EAG's view, the CrIs are too wide to draw that conclusion.

Issue 62

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 106 Paragraph 2: *'The EAG are concerned that applying waning on this "immediate" basis does not reflect the mechanism of action of Ios'*	Please change *'Ios'* to *'IOs'*	Typographical error	The EAG has made the suggested changes.