Single Technology Appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

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 Merck Sharpe & Dohme

2. **Company summary of information for patients (SIP)** from Merck Sharpe & Dohme

3. **Clarification questions and company responses:**
   a. Main response
   b. Additional responses
   c. Scenario analyses excluding estimated osimertinib patient access scheme (PAS) discount

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Roy Castle Lung Cancer Foundation
   b. British Thoracic Oncology Group (and on behalf of National Cancer Research Institute and Royal College of Physicians)
   c. Royal College of Pathologists

5. **External Assessment Report** prepared by BMJ-TAG

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

7. **Company letter on EAG base case assumptions:**
   a. Letter
   b. Updated base case results

8. **External Assessment Group response to company letter on EAG base case assumptions:**
   a. Response
   b. Updated results tables

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Document B

Company evidence submission

March 2024

File name	Version	Contains confidential information	Date
NICE ID3907 Pembrolizumab adjuvant NSLC - Document B [CON]	1.0	Yes	12 March 2024

Contents

Tables and figures

Abbreviations

Abbreviation/acronym	Definition
AE	Adverse Event
AEOSI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
COPD	Chronic Obstructive Pulmonary Disease
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free Survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	EuroQoL-5D
EU	European Union
LS	Least Squares
LCSS	Lung Cancer Specific Survival
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NDRS	National Cancer Registration and Analysis Service
NICE	National Institute for health and Care Excellence
NLCA	National Lung Cancer Audit
NSCLC	Non-small cell lung cancer
OS	Overall Survival
PD-L1/2	Programmed death-ligand 1/2
PET-CT	Positron emission tomography–computed tomography
RCT	Randomised Controlled Trial
SCLC	Small cell lung cancer
SmPC	Summary of Product Characteristics
TNM	Tumour Node Metastasis
TPS	Tumour Proportion Score
UK	United Kingdom
UICC	International Union Against Cancer
WHO	World Health Organisation

Definitions and descriptions of key terms used in the submission

Term	Definition
IA2	Interim analysis 2 corresponding to September 2021 data cut-off
IA3	Interim analysis 3 corresponding to January 2023 data cut-off
Prior Adjuvant Chemotherapy Population	Adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy (the licensed population)

PD-L1 TPS <50% subpopulation	Adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy and whose tumours express programmed death-ligand 1 (PD-L1) with less than 50% (0-49%) tumour proportion score
PD-L1 strong positive	Subgroup of trial participants whose tumour has TPS≥50%
Q3W	Treatment administered on a 3-weekly basis
Q6W	Treatment administered on a 6-weekly basis

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

Summary of the decision problem, technology, and clinical care pathway

- Pembrolizumab has received the Marketing Authorisation as adjuvant treatment of adults with non-small cell lung carcinoma (NSCLC) who are at high risk of recurrence following complete resection and platinum-based chemotherapy, based on the results of the KEYNOTE-091/PEARLS trial. The submission will focus on the subpopulation whose tumours express programmed death-ligand 1 (PD-L1) with less than 50% tumour proportion score (TPS). This reflects the patient group within the licensed population with higher unmet need that will benefit the most from an additional adjuvant treatment.
- There are no other adjuvant treatments that have been routinely commissioned in this subpopulation. Current standard of care for patients with resected early-stage NSCLC after platinum-based chemotherapy is active monitoring. Therefore, the only relevant comparator considered for this appraisal is active monitoring.
- Lung cancer is the second most common cancer type worldwide and constitutes the most common cause of cancer death in the United Kingdom. Lung cancer often remains asymptomatic, or has non-specific symptoms, and undiagnosed until the disease is well advanced. Histology and tumour stage determine optimal management strategy and establish a prognosis for patients. Even at early stage, risk of recurrence and death still remains high.
- Pembrolizumab is anticipated to be used in clinical practice in England as adjuvant therapy for patients with NSCLC at high risk of recurrence (stage IB [T2a ≥ 4 cm] to IIIA - AJCC 7th edition; IIA through IIIB [N2] under the AJCC 8th edition) following complete surgical resection and adjuvant chemotherapy, and PD-L1 biomarker expression with less than 50% tumour proportion score.
- This technology would represent a 'step-change' in the management of the condition by improving the chance of providing patients at early-stage NCSLC with a treatment that can prevent or delay disease recurrence.
- No equity or equality considerations are anticipated.

B.1.1. Decision problem

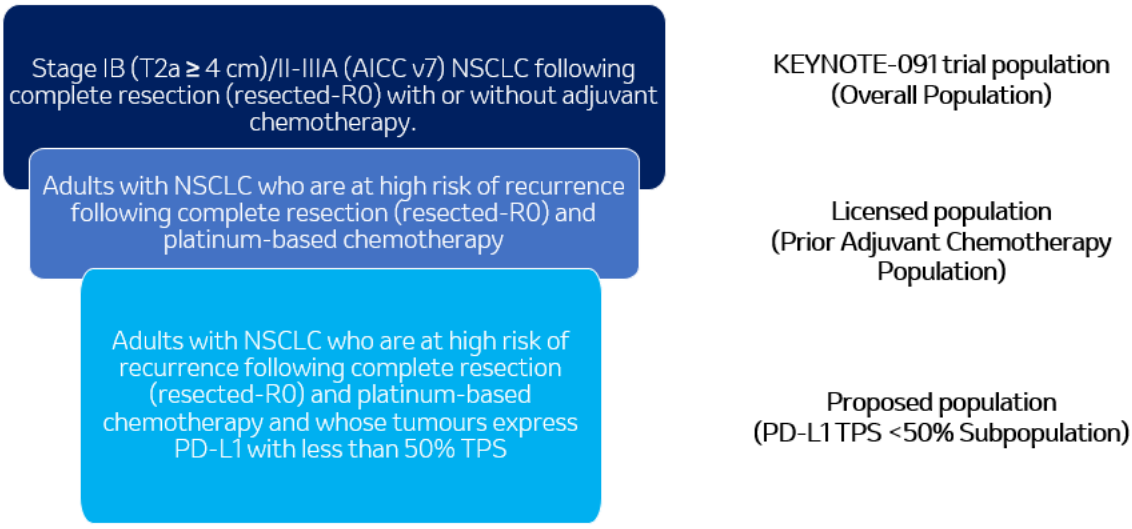
The submission focuses on part of the technology's marketing authorisation which is adults with non-small cell lung carcinoma (NSCLC) who are at high risk of recurrence following

complete resection and platinum-based chemotherapy and whose tumours express programmed death-ligand 1 (PD-L1) with less than 50% (0-49%) tumour proportion score (hereinafter referred to as **PD-L1 TPS <50% subpopulation**). The proposed population is narrower than the marketing authorisation because:

- This population reflects where pembrolizumab provides the most clinical benefit in the adjuvant setting. While the Marketing Authorisation covers the population irrespective of PD-L1 expression, clinical opinion suggested that due to the current uncertainties over the benefits of pembrolizumab in patients whose tumours have PD-L1 biomarker expression with at least a 50% tumour proportion score (PD-L1 TPS ≥50% subpopulation) compared to atezolizumab, pembrolizumab is unlikely to be the preferred option in clinical practice for these patients. Although atezolizumab is currently only commissioned via the Cancer Drugs Fund (CDF) for the PD-L1 TPS ≥50% subpopulation, we consider it likely that this indication will be routinely commissioned in the near future. MSD believe that considering this subpopulation would over-complicate the appraisal.

The definitions of the proposed population, licensed population and the population of the pivotal trial informing this appraisal are provided below.

Figure 1. Definitions of the trial population vs licensed population vs proposed population



Notes: High-risk of recurrence, as per Marketing Authorisation, refers to stage IB (T2a ≥ 4 cm) to IIIA under the AJCC 7th edition (IIA through IIIB [N2] under the AJCC 8th edition).
Abbreviations: AJCC: American Joint Committee on Cancer; NSCLC: Non-small cell lung cancer; PD-L1: programmed death-ligand 1; TPS: tumour proportion score.

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 NSCLC who have undergone complete surgical resection with or without adjuvant chemotherapy	Adults with NSCLC who have undergone complete surgical resection after adjuvant chemotherapy and whose tumours have PD-L1 biomarker expression of less than 50%	Pembrolizumab was approved by the MHRA in the following restricted indication: "*Adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy*.". MSD is seeking reimbursement in the subpopulation whose tumours express PD-L1 with less than 50% tumour proportion score (PD-L1 TPS <50% subpopulation). Based on clinicians' feedback, pembrolizumab would most likely not be used in the subpopulation whose tumours have PD-L1 biomarker expression with at least a 50% tumour proportion score (PD-L1 TPS ≥50%) due to uncertainties associated with the efficacy evidence in these patients compared to available treatments. The submission covers the subpopulation with higher unmet need that can benefit the most from an additional adjuvant option given the lack of treatments available.
Intervention	Pembrolizumab	Pembrolizumab	N/A
Comparator(s)	• Established clinical management without pembrolizumab (that is, active monitoring)	• Established clinical management without pembrolizumab (that is, active monitoring)	N/A

	• Platinum doublet chemotherapy • Durvalumab (subject to NICE appraisal)		• Platinum doublet chemotherapy is not considered a relevant comparator since, as per Marketing Authorisation, the population eligible for pembrolizumab should receive adjuvant platinum-based chemotherapy after surgery and prior to treatment with pembrolizumab as part of the curative treatment. • The peri-adjuvant treatment with durvalumab is not considered a relevant comparator as the patients eligible for pembrolizumab, based on the study design of the pivotal trial (KEYNOTE-091/PEARLS), would not receive immunotherapies prior to surgery and therefore pembrolizumab as adjuvant treatment cannot be compared with peri-adjuvant immunotherapies. Also, while participants in the KEYNOTE-091 trial have been randomised after successful completion of a radical treatment plan, in the perioperative setting participants are randomised prior to initiation of the radical treatment plan. The decision point in the clinical pathway is

	For people whose tumours express PD-L1 with at least a 50% tumour proportion score • Atezolizumab after adjuvant platinum-based chemotherapy (subject to NICE appraisal) For people whose tumours have an EGFR genetic alteration • Osimertinib (subject to NICE appraisal)		therefore not the same between the trials, the KEYNOTE-091 population being a downstream subset of those included in trials of peri-adjuvant treatment. Also, since the NICE appraisal for durvalumab [ID6220] is currently ongoing [(1)], durvalumab is not considered standard of care. It is our understanding that atezolizumab [TA823] [(2)] and osimertinib [TA761] [(3)] are recommended under the CDF and, therefore, they cannot be considered relevant comparators in this appraisal in the respective population in which have been recommended under the CDF. Also, pembrolizumab is not expected to be used in the populations in which atezolizumab and osimertinib received their respective NICE recommendation.
Outcomes	• disease-free survival • event-free survival • overall survival • adverse effects of treatment • health-related quality of life	• disease-free survival • overall survival • adverse effects of treatment • health-related quality of life	The pivotal trial (KEYNOTE-091) informing this submission assessed DFS which is defined as the time from randomization to either the date of disease recurrence or the date of death which are events that may occur in resected patients. Event-free survival (EFS) is not considered a relevant outcome in the evaluation of an adjuvant treatment. EFS has been utilised in trials evaluating the efficacy of perioperative and neoadjuvant treatments as it measures events such as

			progression of disease precluding surgery and inability to resect the tumour which cannot be measured in patients who have undergone complete resection before receiving adjuvant treatment.
Subgroups to be considered	If evidence allows the following subgroups will be considered: • by disease stage • by level of PD-L1 expression	No subgroups have been considered in the submission	The submission already focuses on PD-L1 TPS <50% subpopulation on the basis of clinical opinion around the expected positioning of the technology. Further subgroups not explored for C/E: Subgroups by stage should not be considered separately. Whilst stage was a stratification factor in the KEYNOTE-091 trial (the pivotal trial supporting this appraisal), the sample size of the subgroups by stage in the subpopulation in which MSD is seeking reimbursement would be very small (e.g., 45 and 38 patients with stage IB NSCLC in the pembrolizumab and control arm, respectively), and therefore no valid and reliable conclusions can be drawn about how the effectiveness of the technology might differ across these subgroups. In the licensed population, the confidence intervals around subgroup treatment effects overlapped. Also, current SoC for NSCLC patients after complete surgical resection and adjuvant chemotherapy is the same irrespective of stage of cancer prior to surgery and therefore clinical effectiveness and cost-effectiveness of the technology in these subgroups would

			be evaluated in comparison with same SoC. Furthermore, previous adjuvant treatment submissions to NICE e.g. [TA823] have not included analysis of subgroups by stage [(2)] The submission covers one of the subgroups by PD-L1 status (PD-L1 TPS <50% subpopulation). Therefore, the analysis in any other PD-L1 subgroups (e.g., PD-L1 TPS ≥50) not included in the population proposed in this appraisal is not considered relevant.

Abbreviations: CDF: Cancer Drugs Fund; C/E: cost-effectiveness; EGFR: Epidermal Growth Factor Receptor; MHRA: Medicines & Healthcare products Regulatory Agency; NSCLC: Non-small cell Lung cancer; PD-L1: programmed death-ligand 1; SOC: standard of care; TPS: tumour proportion score.

B.1.2. Description of the technology being evaluated

Pembrolizumab (KEYTRUDA®, MSD) is a humanized monoclonal anti-programmed cell death-1 antibody which binds to the programmed cell death 1 (PD-1) receptor, thereby blocking its interaction with ligands PD-L1 and programmed death-ligand 2 (PD-L2).[4] The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. PD-L1 and PD-L2 are expressed in antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Table 2 presents a description of pembrolizumab for the indication being appraised. The Summary of Product Characteristics (SmPC) is presented in Appendix C. [4]

Table 2. Technology being evaluated

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab is a monoclonal antibody, which binds to the PD-1 receptor, thereby potentiating an immune response to tumour cells.
Marketing authorisation/CE mark status	Application for a Type II variation was submitted to the European Medicines Agency (EMA) in April 2022. Regulatory application to the Medicines & Healthcare Products Regulatory Agency (MHRA) occurred in September 2023 and was based on EC Decision Reliance procedure, following CHMP positive opinion (EMEA/H/C/003820/II/0121) received on 14 September 2023. [5] GB Marketing Authorisation (MA) was obtained in December 2023. [4]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The approved indication is the following: KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy. Pembrolizumab has obtained regulatory approval for the management of the following conditions: • Melanoma • NSCLC • Classical Hodgkin lymphoma (cHL) • Urothelial carcinoma • Head and neck squamous cell carcinoma (HNSCC) • Renal cell carcinoma (RCC) • Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers • Colorectal cancer (CRC)

	• Oesophageal carcinoma • Triple-negative breast cancer (TNBC) • Endometrial carcinoma • Cervical cancer • Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma • Biliary tract carcinoma (BTC) Current SmPC is provided in Appendix C.
Method of administration and dosage	The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W) administered as an intravenous infusion over 30 minutes. For the indication relevant to this appraisal, KEYTRUDA is administered for 18 cycles (Q3W).
Additional tests or investigations	Testing for PD-L1 tumour expression level, measured by the TPS which consists of the proportion of PD-L1–positive tumour cells relative to the total number of viable tumour cells.
List price and average cost of a course of treatment	£2,630 per 100 mg vial.
Patient access scheme (if applicable)	A patient access scheme (PAS) is in place.

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

B.1.3.1. Health condition

Lung cancer is characterised by the formation of malignant cells in the tissue of the lungs, usually the epithelial cells lining the air passages.[6] Lung cancer can be divided into two major classes on the basis of biology, therapy, and prognosis: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[7]

NSCLC constitutes 85 to 88% of all cases of lung cancer in the UK [8]. It comprises two major histological subtypes, generally correlated with the cancer's site of origin, such as squamous cell carcinoma (25% to 30% of lung cancer cases), usually starting near a central bronchus, and non-squamous cell carcinoma, mainly originating in peripheral lung tissues. The latter can be further categorised as adenocarcinoma, the most common type and most frequent subtype among non-smokers, accounting for approximately 40% of cases, and large cell carcinoma (5-10% of lung cancer cases).[9-11]This classification is predictive of responsiveness, improved outcomes, or elevated risk of adverse effects with specific NSCLC treatments and assists in determining the most appropriate patient therapy.[9, 10]

Notably, the prevalence of the different histological subtypes has changed with time, which reflects the temporal change in smoking prevalence.[12]

NSCLC is most commonly staged using the Tumour-Node-Metastasis (TNM) system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) [13] which is based on the primary tumour size and extent (T), location of involved lymph nodes (N), and presence of distant metastases (M).[14] Currently, the eighth edition of the stage classification is used.[15] However, tumour staging in the trial informing this submission was based on the seventh edition (Table 3).[16]

Table 3. Stage grouping according to seventh and eighth edition of TNM staging of lung cancer

Stage group	TNM staging (7th edition)[13]	TNM staging (8th edition)[15]
0	(TisN0M0)	(TisN0M0)
IA	T1a/T1bN0M0	T1a/T1b/T1cN0M0 T1(mi)N0M0
IB	T2aN0M0 (T>3 to 5cm)	T2aN0M0 (T>3 to ≤4cm)
IIA	T1a/T1bN1M0 (T1a ≤2cm) (T1b>2 to 3cm) T2aN1M0 (T>3 to 5cm) T2bN0M0 (T>5 to 7cm)	T2bN0M0 (T>4 to ≤5cm)
IIB	T2bN1M0 (T>5 to 7cm) T3N0M0	T1/T2N1M0 T3N0M0
IIIA	T1/T2N2M0 T3N1/N2M0 T4N0/N1M0	T1/T2N2M0 T3N1M0 T4N0/N1M0
IIIB	T4N2M0 Any T, N3, M0	T1/T2N3M0 T3/T4N2M0 T3/T4N3M0 (stage IIIC)
IV	Any T, Any N, M1a/M1b	Any T, Any N, M1a/M1b Any T, Any N, M1c

Note: Stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC under the AJCC 7th edition (used in the KEYNOTE-091 trial) is equivalent to stage IIA through IIIB (N2) under the AJCC 8th edition.

Staging of lung tumours (I, II, III, or IV) resulting from the combination of TNM descriptors, is based on patient history, physical examination in combination with laboratory and radiological findings (clinical staging), as well as tissue sampling from biopsy (pathological staging); it determines optimal management strategy and establishes a prognosis for patients.[13, 16]

Stage I lung cancer has no lymph-node involvement nor has reached distant organs and can be between 3-4 cm in size. Stages II-III have larger size (more than 7cm in stage III) and may spread to the lymph nodes or to other areas on the same side of the body.[17] Tumour at

these stages has better prognosis than those diagnosed at metastatic stage (stage IV); however, despite the availability of treatments with curative intent, patients frequently experience local and/or distant recurrence.[18]

Lung cancer is often insidious, remaining asymptomatic and undiagnosed until the disease is well advanced, unless chest examination is performed for other reasons.[19]

The most common symptoms associated with NSCLC are cough, haemoptysis, chest and shoulder pain, dyspnoea, hoarseness, weight loss, anorexia, fever, weakness and bone pain, with most of the symptoms being non-specific; diagnosis becomes more difficult in the presence of co-existing respiratory disease such as chronic obstructive pulmonary disease (COPD).[19, 20]

Epidemiology

Lung cancer is the second most common cancer type and the leading cause of cancer death worldwide, accounting for approximately 2.2 million estimated new cases (11.4% of the total number of new cancers) and 1.80 million deaths (representing 18.0% of cancer deaths) in 2020.[21] A greater incidence of new cases has been found in males (incidence rates 32.1 and 16.2 for males and females, respectively).[22]

In the UK, it is the third most common cancer.[23] In England, based on diagnoses registered in 2021 by the RCRD (Rapid Cancer Registration Dataset), 34,478 patients were diagnosed with lung cancer (ICD10 code: C34).[24] While over 40% of the cases were identified at stage IV (Table 4), a similarly high proportion was detected at early stage, with 19.60%, 6.8% and 10.6% of the cases being identified at stage I, II and IIIA, respectively.[24]

Table 4. Cases of lung cancer by stage (AJCC 8th edition) diagnosed in 2021 (ICD-10 code: C34)

Stage at diagnosis (2021)	N (%)
I	6,758 (19.60)
II	2,344 (6.8)
IIIA	3,655 (10.6)
IIIB/C	2,758 (8.0)
IV	14,136 (41.0)
Unknown	4,827 (14.0)
Total	34,478

Source: NCLA report, 2023.[24]

Older age represents the main risk factor for lung cancer (median age of NSCLC at diagnosis: 74 years)[24], along with smoking which has caused 72% of lung cancer cases in the UK, followed by occupational exposures (particularly asbestos) and air pollution.[25] Lung

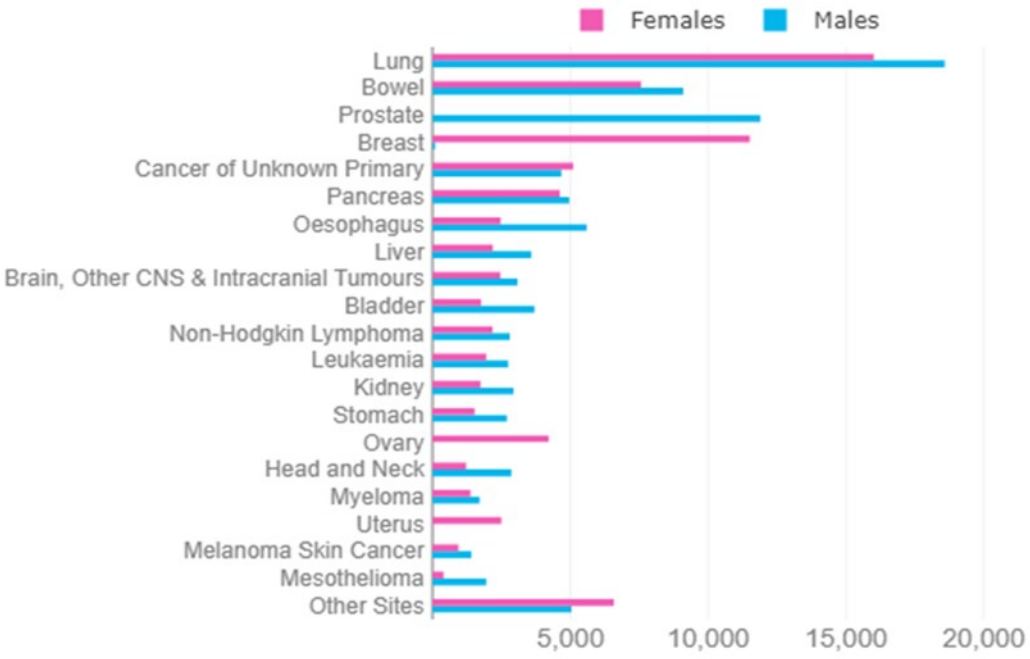
cancer risk also increases in male sex and with deprivation score (around 14,300 cases of lung cancer each year in England have been linked with deprivation).[26]

Lung cancer constitutes the most common cause of cancer death in the UK, accounting for around a fifth (21%) of all cancer deaths in females and males combined (Figure 2).[27] In 2021 28,550 lung cancer deaths have been registered in England and Wales, with about 50% of cases occurring in people aged 75 and over, reflecting the higher incidence of lung cancer and lower survival in this age group.[28] A strong association between lung cancer mortality and deprivation score has been shown in England, as mortality rates have been found 170% higher for males living in the most deprived areas compared with the least deprived, and 176% higher for females.[29] Life expectancy for lung cancer patients depends on several other factors such as stage at diagnosis, sex and performance status.

Despite progress in diagnosis and availability of treatments, 5-year survival remains very poor (26.3%).[30] Overall, only 44.9% of people diagnosed with lung cancer in England have survived their disease for one year or more between 2016 and 2020. [30] Even at early stage the risk of recurrences, either local, regional or distant, is still high (45%, 62% and 76% of patients with stage IB, II and III, respectively [31]), and most of those are distant metastases.[18, 32]

Even though 5-year survival improves when lung cancer is detected at early stage (67.8%, 49.1% and 24.9% for stage 1, 2 and 3, respectively) (Table 5) [30], high unmet need still remains for novel treatments that reduce or delay the risk of recurrence and increase survival rates.

Figure 2. The 20 Most Common Causes of Cancer Deaths, UK, 2018



Source: Cancer Research UK 2023[27]

Table 5. One-year and five-year net survival for adults diagnosed with lung cancer (ICD-10 code: C33 and C34) between 2016 and 2020

1-year age-standardised survival (%)				
Stage I	Stage II	Stage III	Stage IV	All stages
88.1	75.8	52.6	22.5	44.9
5-year age-standardised survival (%)				
67.8	49.1	24.9	8.8	26.3

Source: NHS Digital 2023[30]

B.1.3.2. Treatment pathway

The treatment pathway described below is based on the 'Lung cancer: diagnosis and management (NG122)' NICE guideline (latest update: July 2023).[33]

People with known or suspected lung cancer are offered a contrast-enhanced chest CT or scan to confirm the diagnosis and determine stage of the disease. Biopsy or further imaging (for example, MRI or PET-CT) may be additionally needed for staging and to detect specific markers that can guide treatment strategy, particularly for people who could potentially have treatment with curative intent.

In early-stage NSCLC (stages I-IIIA) main treatments of choice are delivered with curative intent. This is also part of the NICE 2019 quality standards in lung cancer for patients with stage I or II NSCLC and good performance status (WHO 0-1).[34]

If the tumour is resectable, and for patients in which radical treatment is considered suitable based on evaluation of cardiopulmonary fitness and risk of perioperative morbidity, surgery is the preferred treatment option. Lobectomy is the most common surgical option [35] and is recommended by NICE and European guidelines over more limited resection as associated with lower recurrence rate.[36]

According to National Lung Cancer Audit (NLCA) report, around 50% of patients with stage I or II NSCLC received surgery as radical treatment [8] and 25% with stage IIIA.[37]

Neoadjuvant chemotherapy (prior to surgical resection) is not recommended in NICE guideline for people with stage I–II NSCLC that are suitable for surgery. However, in March 2023 nivolumab with chemotherapy has been recommended as an option for the neoadjuvant treatment of resectable NSCLC of at least 4 cm or node positive in adults.[38]

Alternative radical treatment for patients declining surgery or in whom surgery is contraindicated includes radiotherapy, mainly stereotactic ablative radiotherapy (SABR).

The majority of surgical procedures reached complete resection (R0).[39] However, despite the curative intent of surgery, patients with NSCLC face a substantial risk of recurrence due to presence of preoperative micro-metastasis.[18]

Adjuvant chemotherapy after surgery has become an additional treatment option as part of the radical treatment to achieve curative intent. Benefits of adding adjuvant chemotherapy to surgery have been shown in different studies, including meta-analysis.[31, 40-42] Use of adjuvant chemotherapy in tumours with no nodal involvement is more debated and supported by less evidence, with benefits primarily being shown for patients whose tumours were 4 cm in diameter or larger prior to surgical resection.[43] Different combinations of chemotherapy have been associated with survival benefits, although cisplatin-based chemotherapy (e.g., cisplatin + vinorelbine, cisplatin + pemetrexed, cisplatin + gemcitabine) appears to provide better disease-free survival (DFS) outcomes and has been selected by general consensus. Furthermore, most evidence have explored the effects of vinorelbine.[42, 44]

Postoperative cisplatin-based combination chemotherapy is currently offered in England as adjuvant treatment to people with good performance status (WHO 0 or 1) and T1a–4, N1–2, M0 NSCLC.[33]

For tumours with no nodal involvement (T2b–4, N0, M0 with tumours greater than 4 cm in diameter) in patients with performance status 0-1, adjuvant chemotherapy can also be considered.[33]

Pre-existing comorbidity, time from surgery and postoperative recovery are the main factors that determine patients' suitability to the adjuvant treatment and influence therapeutic choice. Patients' choice also plays an important role in the decision-making, particularly in tumours with no lymph node involvement where limited value is perceived.[45] Patients with stage I NSCLC not eligible for neoadjuvant therapy prior to surgery may get upstaged following surgery (approximately 10-15% of early-stage NSCLC patients who undergo surgery) and can benefit from adjuvant treatment.[46] This suggests that, if treatment pathways shift more towards neo-adjuvant treatment for stage II-III patients, there will remain a cohort of patients with a pre-surgical categorisation of stage I who will continue to have unmet need.

There are no additional adjuvant treatments available as part of the established clinical practice for people that undergo surgical resection. Surgery and adjuvant chemotherapy treatment (where suitable) are followed by active monitoring usually consisting of CT scans repeated at regular intervals, every 3-6 months, and becoming less frequent after 1 year. [47]

More detailed recommendations from main clinical guidelines are provided in Table 6. Table 7 presents the treatment recommended by NICE for the indication relevant for this appraisal.

Table 6. Clinical guidelines

NICE NG122 2023[33]	**ESMO 2021[48]**
Recommendations for risk assessment	
• When evaluating surgery as an option for people with NSCLC, consider using a global risk score such as Thoracoscore to estimate the risk of death. Ensure the person is aware of the risk before they give consent for surgery • Seek a cardiology review in people with an active cardiac condition, or 3 or more risk factors, or poor cardiac functional capacity. [2011] • Offer surgery without further investigations to people with 2 or fewer risk factors and good cardiac functional capacity. • Optimise any primary cardiac treatment and begin secondary prophylaxis for coronary disease as soon as possible. • Continue anti-ischaemic treatment in the perioperative period, including aspirin, statins and beta-blockers. • For people with coronary stents, discuss perioperative anti-platelet treatment with a cardiologist. • Consider revascularisation (percutaneous intervention or coronary artery bypass	• In non-metastatic NSCLC, the cardiopulmonary fitness of the patient will determine the choice of treatment. • The risk of postoperative morbidity and mortality can be estimated using risk-specific models, although none have been validated in a cancer population. • Before considering surgical resection, precise assessment of cardiac and pulmonary function is necessary to estimate risk of operative morbidity. • Formal lung function testing should be undertaken to estimate postoperative lung function. For patients with FEV1 and DLCO values >80% of their predicted pulmonary function tests and no other major comorbidities, no further investigations are advised before surgical resection. For others, exercise testing and split lung function are recommended. In these patients, VO_2max can be used to measure exercise capacity and predict postoperative complications.

grafting) before surgery for people with chronic stable angina and conventional indications for revascularisation. • Perform spirometry and transfer factor (TLCO) in all people being considered for treatment with curative intent. • Offer people surgery if they have a forced expiratory volume in 1 second (FEV1) within normal limits and good exercise tolerance. • When considering surgery perform a functional segment count to predict postoperative lung function. • Offer people with predicted postoperative FEV1 or TLCO below 30% the option of treatment with curative intent if they accept the risks of dyspnoea and associated complications. • Consider using shuttle walk testing (using a distance walked of more than 400 m as a cut-off for good function) to assess the fitness of people with moderate to high risk of postoperative dyspnoea. • Consider cardiopulmonary exercise testing to measure oxygen uptake (VO2 max) and assess lung function in people with moderate to high risk of postoperative dyspnoea, using more than 15 ml/kg/minute as a cut-off for good function	• Comorbidities should be evaluated and optimised before surgery • In patients with limited pulmonary function due to emphysema, a lung volume reduction effect may be observed by resection of the lung cancer within emphysematous lung tissue
Recommendations for treatment	
• For people with NSCLC who are well enough and for whom treatment with curative intent is suitable, offer lobectomy (either open or thoracoscopic). • Offer more extensive surgery (bronchoangioplastic surgery, bilobectomy, pneumonectomy) only when needed to obtain clear margins. • Perform hilar and mediastinal lymph node sampling or en bloc resection for all people having surgery with curative intent. • For people with T3 NSCLC with chest wall involvement who are having surgery, aim for complete resection of the tumour using either extrapleural or en bloc chest wall resection. • For people with stage I–IIA (T1a–T2b, N0, M0) NSCLC who decline lobectomy or in whom it is contraindicated, offer radical	• Surgery should be offered to all patients with stage I and II NSCLC as the preferred treatment to all who are willing to accept procedure-related risks. • For patients with a non-centrally located resectable tumour and absence of nodal metastasis on both CT and PET images, surgical resection is recommended. • Lobectomy is still considered the standard surgical treatment of tumours ≥2 cm in size that have a solid appearance on CT. • Lymph node dissection should conform to IASLC specifications for staging. • Either open thoracotomy or VATS access can be carried out as appropriate to the expertise of the surgeon

radiotherapy with stereotactic ablative radiotherapy (SABR) or sublobar resection	• VATS should be the approach of choice in stage I tumours.The non-surgical treatment of choice for stage I NSCLC is SABR. The dose should be to a biologically equivalent tumour dose of ≥100 Gy, prescribed to the encompassing isodose.
• Offer postoperative chemotherapy to people with good performance status (WHO 0 or 1) and T1a–4, N1–2, M0 NSCLC. • Consider postoperative chemotherapy for people with good performance status (WHO 0 or 1) and T2b–4, N0, M0 NSCLC with tumours greater than 4 cm in diameter. • Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy. • For people with stage I–II NSCLC that are suitable for surgery, do not offer neo-adjuvant treatment outside a clinical trial. • Ensure eligible people have the benefit of detailed discussion of the risks and benefits of adjuvant chemotherapy.	• Adjuvant ChT should be offered to patients with resected TNM 8th edition stage IIB and III NSCLC and can be considered in patients with T2bN0, stage IIA resected primary tumour >4 cm. Pre-existing comorbidity, time from surgery and post-operative recovery need to be taken into account in this decision taken in a multidisciplinary tumour board • For adjuvant ChT, a two-drug combination with cisplatin is preferable. […] • When cisplatin administration is not feasible, carboplatin is an accepted alternative. • Although the most frequently studied regimen is cisplatin-vinorelbine, other combinations such as cisplatin and gemcitabine, or docetaxel or pemetrexed (only in adenocarcinoma tumours) could be also feasible. • Carboplatin and paclitaxel is a potential chemotherapy option for T2bN0, stage IIA resected primary tumour >4 cm. • Osimertinib is indicated for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 L858R substitution mutations. • Even if such patients were not included in randomised clinical trials, adjuvant ChT should be considered in patients with R1 resection of stage IIA-IIB-III disease.
Recommendations for follow-up	
• Offer all people with lung cancer an initial specialist follow-up appointment within 6 weeks of completing treatment to discuss ongoing care. Offer regular appointments after this, rather than relying on the person	• NSCLC patients treated with radical intent should be followed for treatment-related complications, detection of treatable relapse or occurrence of second primary lung cancer.

requesting appointments when they experience symptoms • Offer protocol-driven follow-up led by a lung cancer clinical nurse specialist as an option for people with a life expectancy of more than 3 months	Multidisciplinary team assessment is required for feasibility check for treatment of local-regional relapse. • Surveillance every 6 months for 2 years with a visit including history, physical examination and contrast-enhanced • volume chest and abdominal CT scan at least at 12 and 24 months is recommended, with optional [18F]2-fluoro-2-deoxy-D-glucose-PET if required, and thereafter an annual visit including history, physical examination and chest/upper abdominal CT scan in order to detect second primary tumours.

Table 7. Summary of NICE guidance for adjuvant treatment of early-stage NSLC

TA761 (2022)[3]	Osimertinib for use within the CDF as adjuvant treatment after complete tumour resection in adults with stage 1b to 3a non-small-cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations
TA823 (2022)[2]	Atezolizumab for use within the CDF as an option for adjuvant treatment after complete tumour resection in adults with stage 2 to 3a non-small-cell lung cancer (NSCLC) whose: • tumours have the programmed cell death ligand-1 (PD-L1) biomarker expression on 50% or more of their tumour cells and • whose disease has not progressed after platinum-based adjuvant chemotherapy

Abbreviations: CDF: Cancer Drugs Fund.

Unmet need and burden of disease

Survival rates are still poor for early-stage NSCLC patients, despite the progress in early diagnosis and the curative intent of radical treatment. Tumour recurrences (local/regional recurrence or distant metastasis) can develop after surgical resection with significant impact on survival. A meta-analysis by the LACE Collaborative Group showed recurrences occurring in 27% and 57% of patients with stage I-III completely resected NSCLC who received adjuvant chemotherapy at 1 and 5 years after surgery, respectively.[31] Approximately 50% of patients survived at 5 years.[31] In a real-world study, 41% of the patients with stage I-III NSCLC who have undergone a complete surgical resection subsequently developed local or distant recurrence within 23 months of median follow-up.[18] Notably, the majority of the recurrences (~80%, including those that were both local and distant) were distant, which can be life altering for patients as no curative treatment options

are effective at this stage of the disease. Local or regional recurrence can also further progress to distant metastasis.[49].

Furthermore, NSCLC patients with recurrence after complete resection experience worse survival outcomes than patients without recurrence and disease-free interval was shown to be one of the predictors for the post-recurrence survival.[50, 51]

It is therefore paramount to reduce the risk of recurrent disease and prevent or slow disease progression to stages where curative treatments are no longer an option for patients.

Patients with epidermal growth factor receptor (EGFR) mutation-positive NSCLC can now benefit from the addition of osimertinib to the standard of care through CDF.[3] Patients with EGFR mutations represent a small proportion of people with NSCLC, accounting for only 15%.[8] Atezolizumab is available for use within the CDF for patients with stage II to IIIa (AJCC 7th edition) NSCLC whose tumours have the PD-L1 biomarker expression on 50% or more of their tumour cells.[2] In contrast, no other treatment options are available for those patients whose tumours express PD-L1 with less than 50% tumour proportion score.

Current adjuvant chemotherapies offer minimal benefit to reduce risk of recurrence, with an absolute improvement of 5.8% only when compared to surgery alone corresponding to 43% of patients being recurrence-free at 5 years.[31] This results in patients often declining adjuvant chemotherapies as little added value is perceived for a type of treatment with well-known toxicity. UK clinicians have reported that only around 50% of early-stage NSCLC patients currently receive adjuvant chemotherapy, with higher uptake observed in patients with N2 tumours.[45]

Having a recurrence has a significant impact on the quality of life and symptom burden of early-stage NSCLC patients. While patients who remain recurrence-free 2 years after surgery show improvement (e.g., pain scale) or no substantial change in HRQOL, patients with recurrence experience a deterioration across most dimensions of HRQoL such as physical functioning, pain and fatigue.[52]

Even those patients in long-term remission can fear their cancer returning, which can result in stress and anxiety with significant impact on their quality of life.[53-55] Among early-stage NSCLC patients with no evidence of disease recurrence between one to six years post-surgical resection with curative intent, 20% reported clinically significant symptoms of anxiety and 9.6% reported symptoms of depression; the latter was associated with symptoms such as dyspnoea and difficulties in physical functioning.[56]

Dyspnoea is a very common symptom and many patients have reported spending most of the day in bed due to respiratory symptoms.[57, 58]

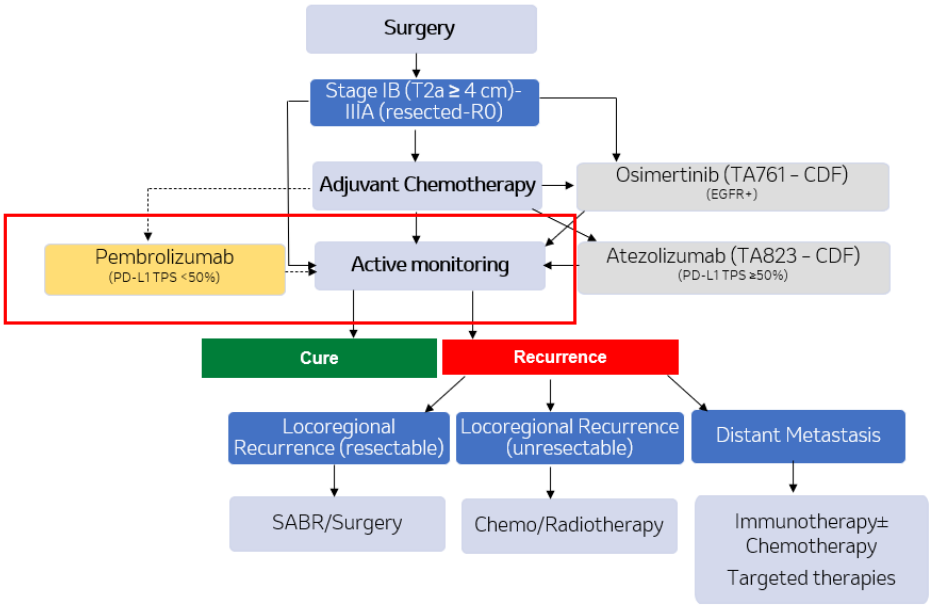
There is an urgent need for innovative treatments at the early stage of lung cancer that can result in desirable survival outcomes without further negative impact on patients' quality of life.

Early-stage NSCLC is equally associated with significant economic burden. The mean per-patient direct costs were found to be higher after disease recurrence (local-regional or distant metastasis/terminal disease phases) than during the disease-free period.[59] The availability of more effective adjuvant therapies would reduce both the downstream costs and human burden associated with recurrence and progression to more advanced disease stages.

Positioning of pembrolizumab relative to the current treatment pathway

Pembrolizumab is anticipated to be used in clinical practice in England as adjuvant therapy for patients with NSCLC at high risk of recurrence (stage IB [T2a ≥ 4 cm] to IIIA under AJCC 7th edition; IIA through IIIB [N2] under the AJCC 8th edition) following complete surgical resection and adjuvant chemotherapy, and PD-L1 biomarker expression with less than 50% tumour proportion score (PD-L1 TPS <50%). In the absence of any recommended adjuvant therapies in this subpopulation as part of the established clinical practice, the comparator considered for this appraisal is active monitoring. Figure 3 shows the proposed positioning of pembrolizumab relative to the current treatment pathway.

Figure 3. Proposed positioning of pembrolizumab relative to the current pathway



Note: Tumour staging is based on TNM staging AJCC 7th edition used in the KEYNOTE-091 trial.
Abbreviations: CDF: Cancer Drugs Fund; EGFR: Epidermal Growth Factor Receptor; NSCLC: Non-small cell Lung cancer; PD-L1: programmed death-ligand 1; TPS: tumour proportion score.

The expected positioning of pembrolizumab in clinical practice is consistent with the results of the phase 3 KEYNOTE-091 trial, the pivotal clinical trial that will inform this submission. KEYNOTE-091 demonstrates that the use of pembrolizumab in the adjuvant setting significantly reduces the risk of recurrence or death compared with placebo in the population that has received adjuvant chemotherapy.

However, clinical consensus indicates that pembrolizumab is not currently expected to become the preferred treatment option in the PD-L1 TPS ≥50% subpopulation. This is due to uncertainties over the efficacy of pembrolizumab compared to atezolizumab, which is currently recommended for use under CDF, in this subpopulation.

According to the advisers at both MSD's UK advisory boards the results of KEYNOTE-091 in the PD-L1 TPS ≥50% subpopulation contradict clinical expectations.[45, 46] It has been established in several advanced lung cancer trials that PD-1 inhibitors have greater efficacy in this group.[60-62] It was suggested that the control arm of KEYNOTE-091 overperformed in this group.

While long-term follow-up data can potentially provide more clarity on the efficacy outcomes in the PD-L1 TPS ≥50% subpopulation, limited unmet medical need that can be addressed by pembrolizumab is currently perceived.
Instead, considering the absence of other adjuvant options in the PD-L1 TPS <50% subpopulation, pembrolizumab has the potential to address the unmet need in these patients.

This technology would represent a 'step-change' in the management of the condition for this subpopulation, by improving the probability of providing NSCLC patients at early-stage with a treatment plan that is genuinely curative.

Introduction of adjuvant pembrolizumab would shift the treatment pathway towards an earlier preventative treatment enabling more patients to benefit from a reduced risk of disease recurrence. Furthermore, introduction of earlier preventative therapy to reduce the risk of metastatic disease and disease recurrence may result in reduced capacity constraints with later line therapies.

B.1.3.3. Treatment setting

Pembrolizumab as adjuvant treatment is expected to be used in secondary care (i.e., hospital setting) based on multidisciplinary team (MDT) or joint clinic team discussion on treatment plans. Patients will receive the treatment as an outpatient (no inpatient stay required) on a 3-weekly cycle or 6-weekly cycle, with duration of administration of 30 minutes per infusion for 18 cycles (if 3-weekly cycle).

B.1.4. Equality considerations

No equity or equality considerations are anticipated.

B.2. Clinical effectiveness

Summary of key clinical effectiveness information

Randomised controlled trial results:

- In the KEYNOTE-091/PEARLS trial, the IA3 results in the PD-L1 TPS <50% subpopulation demonstrated a clinically meaningful benefit associated with pembrolizumab, with median DFS approximately 17 months longer in the pembrolizumab group compared to the placebo group and a 28% reduction in the risk of disease recurrence or death in the pembrolizumab group compared to the placebo group (HR: 0.72 [95% CI: 0.58, 0.89]). The results are consistent with the clinically meaningful DFS improvements observed in the licensed population as well as in the overall trial population. The trial met one of the co-primary endpoints (DFS in the overall population) at IA2 and demonstrated statistical significance.
- Whilst a low number of OS events have occurred (23.1% vs 30.3%), the Overall Survival (OS) analysis in the PD-L1 TPS <50% subpopulation is suggestive of survival benefit that favoured pembrolizumab over placebo (HR: 0.73 [95% CI: 0.55, 0.97]). Final OS analysis is not expected to occur until [redacted], due to slow accrual of OS events in the adjuvant setting.
- HRQoL was measured by EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D. Analysis of the EQ-5D-3L utility score at Week 48 showed no clinically meaningful changes from baseline in either treatment groups; least squares (LS) mean difference of [redacted](95% CI: [redacted]; nominal p=[redacted]).
- The adverse event (AE) summary profile observed for participants treated with pembrolizumab was generally consistent with the known safety profile of this treatment. No new immune-mediated AEs were identified for pembrolizumab in the adjuvant setting. The majority of AEs were Grade 1 or 2.
- KEYNOTE-091/PEARLS (NCT02504372) is a triple-blinded, randomised, placebo-controlled phase III trial that investigates the use of adjuvant pembrolizumab for reducing recurrence risk in patients with stage IB (T ≥ 4 cm)-IIIA (AJCC 7th edition) NSCLC following complete resection with or without adjuvant chemotherapy.
- The data reported in this submission represent the results of the protocol-prespecified interim analysis 3 (IA3 – database cut-off date of 24-JAN-2023) that provides final analysis for DFS and interim analysis for OS. Final OS analysis is event-driven so timings may be subject to change.

Network meta-analysis:

- The KEYNOTE-091 trial provides a robust, head-to-head comparison with the comparator of interest for this appraisal (i.e., active monitoring), therefore no indirect or mixed treatment comparisons were conducted.

Clinical effectiveness conclusions

- KEYNOTE-091 demonstrates that the use of pembrolizumab in the adjuvant setting significantly reduces the risk of disease recurrence or death compared to placebo, which can result in better survival outcomes. Therefore, DFS is a clinically relevant endpoint for early-stage resected NSCLC patients.
- Implementation of adjuvant pembrolizumab would allow shifting of treatment pathways towards earlier preventative treatment have the potential to be genuinely curative, particularly in the PD-L1 TPS <50% subpopulation, a patient group with high unmet medical need that will benefit the most from an additional effective adjuvant treatment option.

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was carried out as per NICE guidance and according to a pre-specified protocol, to identify the clinical evidence, from published and unpublished RCTs, on pembrolizumab and any comparator treatments for the indication of interest for this appraisal as described in Table 1. Full details of the process and methods used are provided in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

The SLR identified a single RCT (KEYNOTE-091) that provided evidence on the clinical effectiveness of pembrolizumab in the patient population relevant to this appraisal (patients with stage IB [T2a ≥ 4 cm] to IIIA [AJCC 7th edition] NSCLC following complete surgical resection and adjuvant chemotherapy, and PD-L1 biomarker expression with less than 50% TPS) (Table 8).

Table 8. Clinical effectiveness evidence

Study	KEYNOTE-091/PEARLS (NCT02504372)[63, 64]
Study design	Phase 3, placebo-controlled, triple-blinded, randomized controlled trial
Population	Stage IB (T2a ≥ 4 cm)/II-IIIA (AICC v7) NSCLC after completion of radical surgery with or without adjuvant chemotherapy. **Efficacy results will be reported for the PD-L1 TPS <50% subpopulation** (adults with non-small cell lung

	carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy and whose tumours express PD-L1 with less than 50% TPS)
Intervention(s)	Pembrolizumab (intravenous)
Comparator(s)	Placebo
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	**Disease-free Survival (DFS)** as assessed locally by the investigator, primary endpoint **Overall Survival (OS),** secondary endpoint **Adverse Events (AEs)** **Health-related Quality of Life (HRQoL)** assessed by EORTC QLQ-C30 (version 3) and EQ-5D-5L
All other reported outcomes	N/A

Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L: EuroQoL; N/A: not applicable; NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1; TPS: tumour proportion score.

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

Table 9. Summary of trial methodology

Study name	KEYNOTE-091/PEARLS (NCT02504372)
Trial design	Phase 3, randomized, triple-blinded, placebo-controlled, multicentre study
Eligibility criteria for participants	Inclusion criteria • Male and female participants at least 18 years of age • Pathological diagnosis of AJCC v7 Stage IB (T2a ≥4 cm), Stage II, or Stage IIIA NSCLC confirmed after complete surgical resection (lobectomy, sleeve lobectomy, bi-lobectomy, or pneumonectomy) as documented in the pathology report. Resection margins proved microscopically free (R0). • Availability of tumour sample obtained at surgical resection for PD-L1 IHC expression assessment. Participants were eligible to participate regardless of the level of PD-L1 status. • Adjuvant chemotherapy was not mandatory but considered for patients with AJCC v7 Stage IB (T2a

	≥4 cm) and strongly recommended for Stage II and IIIA and was administered according to national and local guidelines. Patients who received more than 4 cycles of adjuvant therapy were not eligible. • ECOG performance status 0 or 1. <u>Exclusion criteria</u> • Evidence of disease at clinical examination and baseline radiological assessment within 12 weeks prior to the randomization date. • Received or planned to receive neoadjuvant or adjuvant radiotherapy and/or neoadjuvant chemotherapy for the current malignancy. • Prior treatment with an anti-PD-1, anti-PD-L1/2, anti-CD137, CTLA-4 modulators, or any other immune-modulating agents. • Surgery-related or chemotherapy-related toxicity (non-hematologic toxicity resolved to Grade 1 was acceptable, with the exception of alopecia, fatigue, neuropathy, and lack of appetite/nausea).
Settings and locations where the data were collected	Multinational multicentre study conducted at 206 centres in 29 countries. 53 patients were recruited in the UK across 14 sites.
Trial drugs	Intervention arm: pembrolizumab, 200 mg every 3 weeks (Q3W) for 18 cycles (1 year) Comparator arm: placebo Q3W for 18 cycles (1 year)
Primary outcomes	DFS, as assessed locally by the investigator, in the overall population and PD-L1 strong positive subgroup (TPS≥50%)
Other outcomes used in the economic model/specified in the scope	• OS • AEs • HRQoL assessed by EORTC QLQ-C30 (version 3), EORTC QLQ-LC13 and EQ-5D-5L
Pre-planned subgroups	• Age (< 65 vs. ≥ 65) • Sex (Male vs. Female) • Race (White vs. All Others) • Region (EU vs. Non-EU) • Region (Western Europe vs. Eastern Europe vs. Rest of the World vs. Asia) – stratification factor • Stage (IB vs. II vs. IIIA) – stratification factor • Adjuvant Chemotherapy (No vs. Yes) – stratification factor • Smoking Status (Never Smoker vs. Former Smoker vs. Current Smoker) • Histology (Squamous vs. Non-squamous) • ECOG Performance Status (0 vs. 1) • EGFR Mutation Status (N vs. Y vs. Unknown) • PD-L1 Status – stratification factor

	○ TPS < 1% vs. TPS = 1-49% vs. TPS ≥ 50% ○ TPS < 1% vs. TPS ≥ 1% ○ TPS < 1% vs. TPS ≥ 50%

Abbreviations: AE: Adverse Events; AJCC: American Joint Committee on Cancer; DFS: Disease-free Survival; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal Growth Factor Receptor; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D: EuroQoL-5D; HRQoL: Health-related quality of life; NSCLC: non-small cell lung cancer; OS: Overall Survival; PD-L1: programmed death ligand 1; TPS: tumour proportion score; UK: United Kingdom.

B.2.3.1. Summary of the methodology of the KEYNOTE-091 study

Trial design

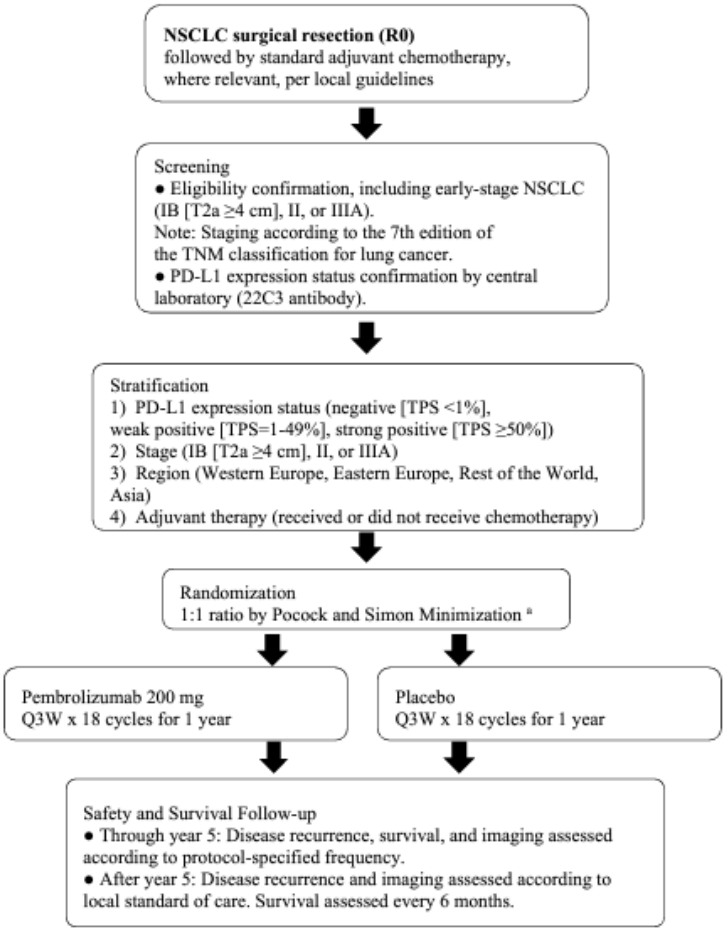
KEYNOTE-091 is a Phase 3, randomized, triple-blinded, placebo-controlled, multicentre study to evaluate the efficacy and safety of pembrolizumab versus placebo in participants with Stage IB (T2a ≥4 cm), II, or IIIA (AJCC 7th edition) NSCLC who have undergone complete resection followed by standard adjuvant chemotherapy where appropriate as per relevant local guidelines. Approximately 1,180 participants were planned to be randomized in a 1:1 ratio to receive either pembrolizumab 200 mg or placebo every three weeks (Q3W) for approximately 1 year (18 infusions).

Participants received the assigned study intervention until completion of 18 infusions, disease recurrence, or one of the discontinuation criteria was met.

Follow-up assessment was performed according to ESMO guidelines every 12 weeks for the first year after randomization, every 6 months in years 2 and 3, annually up to the end of year 5, and according to the local standard of care thereafter. The disease recurrence was still collected beyond the 5th year. Participants were evaluated with radiographic imaging (contrast-enhanced chest and upper abdomen CT scan and contrast-enhanced brain CT scan or MRI only if clinically indicated) to assess tumour recurrence. All images were evaluated by the local principal investigator to assess DFS using RECIST version 1.1. AEs were monitored throughout the study and graded in severity according to the guideline outlined in the NCI CTCAE, Version 4.03.

The UICC/AJCC 7th edition of TNM staging for lung cancer was in place at the time of study initiation; for consistency, this edition was used in the determination of cancer staging for eligibility throughout the study. The study design is depicted in Figure 4.

Figure 4. KEYNOTE-091 Study design



Abbreviations: NSCLC: non-small cell lung cancer; PD-L1: programmed death ligand 1; Q3W: every 3 weeks; R0:no residual tumour; TNM: tumour node metastasis; TPS: tumour proportion score.
Source: Data on File. KEYNOTE-091 IA3 Clinical Study Report [65]

Assignment, randomisation, and blinding

After verification of eligibility and central confirmation that a result for PD-L1 status test could be obtained, eligible patients were randomized at 1:1 ratio into two triple blinded, treatment arms (pembrolizumab or placebo). Randomization was performed centrally through the Interactive Voice Response System (IVRS). At the end of the randomization procedure, the treatment was randomly allocated to the patients through the IVRS using minimization methods and based on the following stratification factors:

- Disease stage (IB vs II vs IIIA);
- Adjuvant chemotherapy (no adjuvant chemotherapy versus adjuvant chemotherapy);
- PD-L1 status: negative (TPS=0%) versus weak positive (TPS=1-49%) versus strong positive (TPS≥50%);

- Region (Western Europe versus Eastern Europe versus the Rest of the world versus Asia).

Patients not receiving adjuvant chemotherapy were randomized and dosed with pembrolizumab/placebo within 12 weeks of their surgery date. Participants who received adjuvant chemotherapy started adjuvant chemotherapy within 12 weeks of their surgery date and were randomized and dosed with pembrolizumab/placebo at least 3 but no more than 12 weeks from the last dose of chemotherapy (Day 1 of last cycle).

As a triple-blinded trial, neither the treatment arm nor its description was provided to the investigator, the Sponsor, European Organization for Research and Treatment of Cancer (EORTC) staff, CRO, patients and site staff.

Eligibility criteria

Key eligibility criteria are provided in Table 9. Full list of eligibility criteria is available in Appendix M.

Settings and locations where the data were collected

KEYNOTE-091 is a multinational multicentre study that was conducted at 206 centres in 29 countries including countries in Europe (20), Asia (e.g., Israel, Japan, Republic of Korea, Turkey), Australia and Canada. 53 patients were recruited in the United Kingdom (UK) across 14 sites.

Trial drugs and concomitant medications

- Interventional arm: pembrolizumab 200 mg, intravenously (IV), every 3 weeks [Q3W] for up to 18 cycles (approximately 1 year);
- Comparator arm: placebo 0 mg, intravenously (IV), every 3 weeks [Q3W] for up to 18 cycles (approximately 1 year). The placebo was administered in the same manner as the investigational product.

In both arms, treatment was administered for a maximum of 18 infusions for approximately one year, unless one of the withdrawal criteria applies. In case of delay in scheduled administration, the treatment could continue beyond 1 year in order to complete the 18 infusions.

Participants could discontinue from study treatment but remained in the trial for follow-up to be assessed for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Outcomes assessed

Primary outcomes

- DFS, as assessed locally by the investigator, in the overall population and in the PD-L1 strong positive subgroup (TPS≥50%).

DFS is calculated as the time from randomization to either the date of disease recurrence or the date of death (whatever the cause).

Recurrence of disease can be a loco-regional recurrence, a distant (metastatic) recurrence or a second primary. NSCLC and second malignancies were considered to be events.

Secondary outcomes

- DFS in the PD-L1 positive population (TPS≥1%).
- OS in the overall population, in the PD-L1 strong positive subgroup (TPS≥50%) and in the PD-L1 positive population (TPS≥1%).

OS is defined as the time from the date of randomization to the date of death, whatever the cause.

The follow-up of patients still alive was censored at the moment of last visit/contact.

- Lung Cancer Specific Survival (LCSS)

LCSS is calculated as the time from randomization to the date of death (due to lung cancer specifically). The follow-up of patients still alive are censored at the moment of last visit/contact. Patients who die from causes other than lung cancer are censored at the time of death. LCSS was not analysed at IA3 and will be analysed when the data becomes appropriately mature.

- Adverse events (AEs)

The investigator assessed whether those events were drug related (reasonable possibility, no reasonable possibility) and the assessment was recorded in the database for all AEs.

Exploratory outcomes

HRQOL as assessed by EORTC Quality of Life Questionnaire C-30 (QLQ-C30), EORTC QLQ-LC13 and EQ-5D-5L.

Follow-up assessment

Follow up assessment is performed every twelve weeks during the first year after randomization, every six months during the second and third year and then yearly for year four and five, following the imaging workup schedule. Thereafter, the imaging work-up

should be performed at least yearly up to year ten. The disease recurrence will still be collected beyond the fifth year.

Survival

All patients who discontinued study intervention, regardless the reason of discontinuation, move into the Survival Follow-up Phase and should be contacted by telephone every twelve weeks (+/- two weeks) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Participants should continue the follow-up visits according to the protocol. After year five, survival follow-up will be conducted every six months by telephone. The reference date for contacting patients for survival follow-up will follow the same schedule as the imaging schedule (Day 1 of infusion 1 [visit 1]).

Health-related quality of life

EORTC QLQ-C30 version 3, EORTC QLQ-LC13 and EQ5D questionnaires are filled in every twelve weeks (+/- three weeks), during the first year after randomization (starting on day 1 of visit 1); every six months (+/- four weeks) during the second year and then yearly (+/- four weeks) until year five. HRQoL data must be collected regardless of the patient's progression status; no further collection is required beyond the fifth year.

Baseline characteristics of trial participants

The demographic and baseline characteristics of the licensed population (hereinafter referred to as Prior Adjuvant Chemotherapy Population) and the subpopulation in which reimbursement is sought were generally representative of the patients with early-stage NSCLC in the UK. Demographic and baseline characteristics were balanced across the treatment groups.

Approximately 86% of trial participants in both arms received prior adjuvant chemotherapy. In the Prior Adjuvant Chemotherapy Population, over 70% of the tumours had PD-L1 TPS <50% (Table 11).

Slightly less than half of the participants were 65 years of age or older and nearly 70% in both arms were male. The majority of participants were white and from Europe. More than 60% of tumours in both arms had non-squamous histology. Approximately 12% of participants had Stage IB disease and more than half had Stage II disease. Participants characteristics by treatment arm for the PD-L1 TPS <50% subpopulation are presented in Table 10. Participants characteristics for the licensed population are presented in Table 11.

Table 10. Participant Characteristics – PD-L1 TPS < 50% Subpopulation (ITT Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	363		363		726	
Sex						
Male	[redacted]		[redacted]		[redacted]	
Female	[redacted]		[redacted]		[redacted]	
Age (Years)						
< 65	[redacted]		[redacted]		[redacted]	
>= 65	[redacted]		[redacted]		[redacted]	
	[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	
Range	[redacted]		[redacted]		[redacted]	
Race						
Asian	[redacted]		[redacted]		[redacted]	
Black Or African American	[redacted]		[redacted]		[redacted]	
Multiple	[redacted]		[redacted]		[redacted]	
American Indian Or Alaska Native White	[redacted]		[redacted]		[redacted]	
Mestiza	[redacted]		[redacted]		[redacted]	
Mixed Race	[redacted]		[redacted]		[redacted]	
White Black Or African American	[redacted]		[redacted]		[redacted]	
Other	[redacted]		[redacted]		[redacted]	
White	[redacted]		[redacted]		[redacted]	
Missing	[redacted]		[redacted]		[redacted]	
Age (Years)						
< 70	[redacted]		[redacted]		[redacted]	
>= 70	[redacted]		[redacted]		[redacted]	
Age (Years)						
< 65	[redacted]		[redacted]		[redacted]	
65 - 74	[redacted]		[redacted]		[redacted]	
75 - 84	[redacted]		[redacted]		[redacted]	
Geographic Region: EU						
EU	[redacted]		[redacted]		[redacted]	
Non-EU	[redacted]		[redacted]		[redacted]	
Geographic Region: Asia						
East Asia	[redacted]		[redacted]		[redacted]	
Non-East Asia	[redacted]		[redacted]		[redacted]	
Region						
Western Europe	[redacted]		[redacted]		[redacted]	
Eastern Europe	[redacted]		[redacted]		[redacted]	

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Rest of World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 Status (Stratification)						
<1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-49%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage at Baseline per AJCC V7						
IB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking Status						
Never Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Former Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline ECOG						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology						
Squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-squamous	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EGFR Mutation Status						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALK Mutation Status						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD=Standard deviation.						
Database Cutoff Date: 24JAN2023						

Abbreviations: AJCC: American Joint Committee on Cancer; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal Growth Factor Receptor; EU: European Union; PD-L1: Programmed death-ligand 1; SD: standard deviation.
Source: Data on File. KEYNOTE-091 IA3 Statistical Report. [66]

Table 11. Participant Characteristics – Prior Adjuvant Chemotherapy Population (ITT Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	506		504		1,010	
Sex						
Male	339	(67.0)	347	(68.8)	686	(67.9)
Female	167	(33.0)	157	(31.2)	324	(32.1)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Age (Years)						
< 65	264	(52.2)	252	(50.0)	516	(51.1)
>= 65	242	(47.8)	252	(50.0)	494	(48.9)
Mean	63.3		63.6		63.4	
SD	8.1		7.9		8.0	
Median	64.0		64.5		64.0	
Range	35 to 80		37 to 84		35 to 84	
Race						
Asian	88	(17.4)	89	(17.7)	177	(17.5)
Black Or African American	0	(0.0)	3	(0.6)	3	(0.3)
Multiple	4	(0.8)	1	(0.2)	5	(0.5)
American Indian Or Alaska Native White	1	(0.2)	0	(0.0)	1	(0.1)
Mestiza	1	(0.2)	0	(0.0)	1	(0.1)
Mixed Race	1	(0.2)	0	(0.0)	1	(0.1)
White Black Or African American	1	(0.2)	1	(0.2)	2	(0.2)
Other	6	(1.2)	1	(0.2)	7	(0.7)
White	387	(76.5)	392	(77.8)	779	(77.1)
Missing	21	(4.2)	18	(3.6)	39	(3.9)
Age (Years)						
< 70	384	(75.9)	382	(75.8)	766	(75.8)
>= 70	122	(24.1)	122	(24.2)	244	(24.2)
Age (Years)						
< 65	264	(52.2)	252	(50.0)	516	(51.1)
65 - 74	211	(41.7)	222	(44.0)	433	(42.9)
75 - 84	31	(6.1)	30	(6.0)	61	(6.0)
Geographic Region: EU						
EU	343	(67.8)	342	(67.9)	685	(67.8)
Non-EU	163	(32.2)	162	(32.1)	325	(32.2)
Geographic Region: Asia						
East Asia	87	(17.2)	87	(17.3)	174	(17.2)
Non-East Asia	419	(82.8)	417	(82.7)	836	(82.8)
Region						
Western Europe	261	(51.6)	266	(52.8)	527	(52.2)
Eastern Europe	105	(20.8)	96	(19.0)	201	(19.9)
Rest of World	53	(10.5)	55	(10.9)	108	(10.7)
Asia	87	(17.2)	87	(17.3)	174	(17.2)
PD-L1 Status (Stratification)						
<1%	198	(39.1)	198	(39.3)	396	(39.2)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
1-49%	165	(32.6)	165	(32.7)	330	(32.7)
>=50%	143	(28.3)	141	(28.0)	284	(28.1)
Stage at Baseline per AJCC V7						
IB	60	(11.9)	57	(11.3)	117	(11.6)
II	283	(55.9)	295	(58.5)	578	(57.2)
IIIA	163	(32.2)	150	(29.8)	313	(31.0)
IV	0	(0.0)	2	(0.4)	2	(0.2)
Smoking Status						
Never Smoker	80	(15.8)	57	(11.3)	137	(13.6)
Former Smoker	362	(71.5)	375	(74.4)	737	(73.0)
Current Smoker	64	(12.6)	72	(14.3)	136	(13.5)
Baseline ECOG						
0	326	(64.4)	292	(57.9)	618	(61.2)
1	180	(35.6)	212	(42.1)	392	(38.8)
Histology						
Squamous	157	(31.0)	184	(36.5)	341	(33.8)
Non-squamous	349	(69.0)	320	(63.5)	669	(66.2)
EGFR Mutation Status						
N	190	(37.5)	192	(38.1)	382	(37.8)
Y	36	(7.1)	30	(6.0)	66	(6.5)
Unknown	280	(55.3)	282	(56.0)	562	(55.6)
ALK Mutation Status						
N	196	(38.7)	166	(32.9)	362	(35.8)
Y	6	(1.2)	6	(1.2)	12	(1.2)
Unknown	304	(60.1)	332	(65.9)	636	(63.0)
Database Cutoff Date: 24JAN2023						

Abbreviations: AJCC: American Joint Committee on Cancer; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal Growth Factor Receptor; EU: European Union; PD-L1: Programmed death-ligand 1; SD: standard deviation.
Source: Data on File. KEYNOTE-091 IA3 Statistical Report. [66]

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

Objectives, hypotheses, and endpoints

Study objective and endpoints are described in Table 12.

Table 12. KEYNOTE-091 study objectives, hypotheses, and endpoints

Objective/Hypothesis	Endpoint(s)
Primary	
• To prospectively investigate whether adjuvant treatment with pembrolizumab after completion	• DFS in the overall population;

of radical surgery (lobectomy/pneumonectomy) with or without standard adjuvant chemotherapy for AJCC v7 stage IB (T ≥ 4 cm) -II-IIIA NSCLC patients improves DFS, as assessed locally by the investigator, compared to placebo in the PD-L1 strong positive subgroup (TPS≥50%) or overall population.	• DFS in the PD-L1 strong positive subgroup. With the use of primary and dual-primary endpoints, if either of the tests in the primary or dual-primary endpoint is significant, the study can be declared successful in their respective population or sub-population.
Secondary	
• To prospectively compare DFS as assessed by the investigator in the PD-L1 positive population (TPS≥1%);	• DFS in the PD-L1 positive population;
• To prospectively determine and compare OS in the PD-L1 strong positive and overall population; • To prospectively determine and compare OS in the PD-L1 positive population;	• OS in the overall population; • OS in the PD-L1 strong positive subgroup; • OS in the PD-L1 positive population;
• To prospectively determine and evaluate the LCSS in the whole population irrespective of PD-L1 status;	• LCSS in the overall population;
• To prospectively assess the safety of pembrolizumab after radical surgery followed by standard adjuvant chemotherapy.	• Toxicity according to CTCAE version 4.03.
Tertiary/Exploratory	
• To prospectively assess EQ-5D health state profiles at pre-specified time points; • To prospectively assess Health-related Quality of Life (HRQOL);	• Health-related Quality of Life (HRQOL);
• To evaluate the pharmacokinetics (PK) of pembrolizumab in this patient population to determine the pembrolizumab exposure-response relationships for measures of effectiveness, toxicity, and pharmacodynamic biomarkers in the study population;	• Pharmacokinetics (PK) of pembrolizumab in this patient population;
• To evaluate the development of anti-drug antibodies (ADA) against pembrolizumab (immunogenicity evaluation); • To assess and describe the quality assurance for surgery; • To prospectively assess genetic alterations and biomarkers of immunological pathways with outcome; • To prospectively assess DNA mutational burden and nanostring RNA analysis with outcome;	• Anti-drug antibodies (ADA) against pembrolizumab (immunogenicity evaluation); • Quality assurance for surgery; • Exploratory assessment of predictive biomarkers and immune dynamics (Translational research).

• To evaluate these treatments in the elderly (age ≥70 years old); • To prospectively study the influence of dose and duration of adjuvant chemotherapy on outcome.	

Abbreviations: AJCC: American Joint Committee on Cancer; DNA: deoxyribonucleic acid; DFS: disease-free survival; EQ-5D: EuroQol-5D; HRQoL: health-related quality of life; LCSS: Lung Cancer Specific Survival; NSCLC: non-small cell lung cancer; OS: overall survival; PD-L1: programmed death ligand 1; RNA: ribonucleic acid; TPS: tumour proportion score. Source: Data on File. KEYNOTE-091 Clinical Study Protocol. [67]

Analysis populations

Efficacy analysis population

- Intention-to-treat population (ITT) (N=1,177): All randomized patients were analysed in the arm they were allocated by randomisation.

The primary analyses of the primary and secondary efficacy endpoints (DFS and OS) were performed on all randomized patients according to the ITT principle.

The ITT population for this study in the Overall Population includes 590 in the pembrolizumab arm and 587 in the placebo arm.

- All-participants-as-treated (APaT) population (N=1,161): all randomised participants who received at least one dose of study treatment is used.

This population is used for summaries on drug exposure and study treatment compliance. The APaT population for this study in the Overall Population includes 580 in the pembrolizumab arm and 581 in the placebo arm.

- PRO full analysis set (FAS) population: all randomised participants who received at least one dose of study treatment and completed at least one assessment for the respective PRO questionnaire/scale anytime during the period under investigation.

Safety analysis population

Analysis for toxicity was based on APaT population (N=1,161).

These populations (for both efficacy and safety analyses) are also applicable to the predefined PD-L1 subgroups and to the subpopulation indicated in the licence.

Statistical methods for efficacy analyses

Estimates of the median DFS and OS were obtained by the Kaplan Meier technique. The 95% confidence interval (CI) for the median were calculated using the reflected CI method. Estimates of the event-free rate at a fixed time point were obtained using the Kaplan Meier technique and 95% CI were calculated by the Greenwood's formula for standard deviation.

Estimates of hazard ratios and their 95% CI were obtained by Cox regression with the Kaplan Meier curves drawn for both the experimental and control arms on the same plot.

The DFS and OS were analysed by a Cox Proportional Hazard Regression with treatment adjusted by the following covariates: stratification factors including stage, PD-L1 expression, adjuvant chemo, regions, and additional factors including histology and smoking status. Permutation test was used as a primary test for DFS to compare the experimental versus the control arm. The Wald test without permutation of allocation sequence was used as a supportive analysis for DFS, but as a primary test for OS. The hazard ratios and corresponding 95% CIs were estimated using the multivariate Cox regression model stated above (using Efron's tie-handling method).

Statistical methods for safety analyses

The worst grade of toxicity/adverse events observed over the whole treatment period according to CTCAE version 4.03 was displayed. In the primary analysis, no formal statistical analysis was performed to compare toxicity between arms. Only frequencies and percentages for each treatment arm were provided for adverse experiences (specific terms and system organ class).

Two interim analyses (IAs) and one final analysis (FA) for DFS were planned in the study. At the time of each DFS analysis, OS analysis is performed as well. Three additional analyses for OS alone were planned after the DFS FA. However, the timing of interim analyses may be altered if events accrue at a substantially different rate than anticipated (e.g., if the event accumulation is much slower than expected). Currently, two additional analyses for OS alone after DFS FA are anticipated.

All DFS analyses are event-driven. The timing for IA1 and 2 were determined by the number of DFS events in the PD-L1 strong positive population, and the final DFS analysis (IA3) was conducted when the target DFS event numbers were reached in both populations, i.e. approximately 141 DFS events in the PD-L1 strong positive population and approximately 551 DFS events in the whole population.

Beyond the final analysis of DFS (IA3), all OS analyses are OS event-driven. The timing for OS interim analyses will be determined by the OS event numbers in the PD-L1 strong positive population. The final OS analysis will be conducted when the target OS event numbers are reached in both PD-L1 strong positive and PD-L1 whole populations.

In case only one of the primary DFS hypotheses is significant at the time of IAs, then the significant result is declared in the corresponding population or subgroup. The other primary

DFS hypothesis was tested according to the maturity of the next test, by using the available nominal alpha.

Summary of the statistical methods is provided in Table 13.

Table 13. Summary of KEYNOTE-091 study statistical methods

Analysis populations	Efficacy analysis population • Intention-to-treat population (N=1,177): All randomized patients were analysed in the arm they were allocated by randomisation. • All-participants-as-treated (APaT) population (N=1,161): all randomised participants who received at least one dose of study treatment is used. • PRO full analysis set (FAS) population: all randomised participants who received at least one dose of study treatment and completed at least one assessment for the respective PRO questionnaire/scale anytime during the period under investigation. Safety analysis population • APaT population (N=1,161)
Statistical methods for key efficacy analyses	The DFS and OS were analysed by a Cox Proportional Hazard Regression with treatment adjusted by the following covariates: stratification factors including stage, PD-L1 expression, adjuvant chemo, regions, and additional factors including histology and smoking status. Permutation test was used as a primary test for DFS to compare the experimental versus the control arm. Estimates of the median DFS and OS were obtained by the Kaplan Meier technique.
Statistical methods for key safety analyses	In the primary analysis, no formal statistical analysis was performed to compare toxicity between arms.
Interim and final analyses	Two interim analyses (IAs) and one final analysis (FA) for DFS were planned in the study. At the time of each DFS analysis, OS analysis is performed as well. Currently, two additional analyses for OS alone after DFS FA are anticipated. All DFS and OS analyses are event-driven.
Multiplicity	Bonferroni adjustment is adopted, by initially splitting alpha equally to test DFS, i.e., 1-sided alpha = 1.25% is allocated to the whole population and 1-sided alpha = 1.25% is allocated to the PD-L1 strong positive. The study uses the graphical method of Maurer and Bretz to provide strong multiplicity control for multiple hypotheses as well as interim efficacy analyses.
Sample size and power	It was calculated that approximately 1,180 participants would need to be randomized in a 1:1 ratio into the experimental arm and the control arm.

	Based on a target number of ~551 events at final analysis (FA), the study was designed to have ~86% power at alpha=1.25% (one-sided) and ~92% power at alpha=2.5% (one-sided) to detect 25% reduction in DFS (HR=0.75) for the whole population.

Abbreviations: DFS: disease-free survival; HR: hazard ratio; OS: overall survival.

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

A quality assessment of the KEYNOTE-091 trial was performed using the Cochrane risk-of-bias tool for randomised trials (ROB-2) [68]. Full details of the SLR, including methods and results can be found in Appendix D.

B.2.6. Clinical effectiveness results of the relevant studies

The data presented in this submission represent the results of the protocol-prespecified interim analysis 3 (IA3), with a database cutoff date of 24-JAN-2023. Results are reported for the subpopulation in which reimbursement is sought (PD-L1 TPS <50% - full definition available in Table 14 and in the abbreviations table). Where not available, and if no substantial differences are expected, results are presented for the licensed population (Prior Adjuvant Chemotherapy Population – full definition available in Table 14 and in the abbreviations table).

ITT Population (please see B.2.4 for the definition) mentioned in any of the tables below refers to the analysis population used for the efficacy analysis. This analysis population has been used for PD-L1 subgroups as well, including the PD-L1 TPS <50%, and for the licensed population.

Table 14. Definition and patient numbers of populations discussed in B.2.6 and B.2.10

Population	Definition	Patient numbers in KEYNOTE-091
Overall Population (KEYNOTE-091 trial population)	Stage IB (T2a ≥ 4 cm)/II-IIIA (AICC v7) NSCLC following complete resection (resected-R0) with or without adjuvant chemotherapy.	1,177
Prior Adjuvant Chemotherapy Population (Licensed population)	Adults with NSCLC who are at high risk of recurrence following complete resection (resected-R0) and platinum-based chemotherapy.	1,010
PD-L1 TPS <50% Subpopulation (Proposed population)	Adults with NSCLC who are at high risk of recurrence following complete resection (resected-R0) and platinum-	726

	based chemotherapy and whose tumours express PD-L1 with less than 50% (0-49%) TPS.	

Notes: High-risk of recurrence, as per Marketing Authorisation, refers to TNM stage IB (T2a ≥ 4 cm) to IIIA under the AJCC 7th edition used in KEYNOTE-091.
Abbreviations: AJCC: American Joint Committee on Cancer; NSCLC: Non-small Cell Lung Cancer; PD-L1: programmed death-ligand 1; TPS: tumour proportion score.

B.2.6.1. Patient Disposition

A total of 1,177 participants (590 in the pembrolizumab group and 587 in the placebo group) were randomized and included in the ITT population for the Overall Population. As of the database cut-off date (IA3), no participants were receiving study medication. The proportion of participants who completed study medication was lower in the pembrolizumab group (51.7%) compared with the placebo group (65.6%). Details of patient disposition can be found in Appendix D.2.

B.2.6.2. Exposure of prior adjuvant chemotherapy

Prior adjuvant chemotherapy use across the treatment groups was balanced; approximately 86% (1,010/1,177) of trial participants in both treatment groups received adjuvant chemotherapy. The most common (>10% of participants) agents used in the pembrolizumab group compared with placebo were cisplatin/vinorelbine (40.8% vs 42.6%), carboplatin/vinorelbine (13.7% vs 11.9%), and carboplatin/paclitaxel (10.2% vs 12.8%). The median duration of exposure to prior adjuvant chemotherapy was similar in both treatment groups (Table 15).

Table 15. Summary of Exposure of Prior Adjuvant Chemotherapy – Prior Adjuvant Chemotherapy Population

	Pembrolizumab (N=506)	**Placebo (N=504)**
Duration on Therapy (days)		
Mean	71.2	72.5
Median	71.0	72.0
SD	19.67	19.47
Range	1.0 to 124.0	1.0 to 133.0
Number of Cycles		
Mean	3.7	3.7
Median	4.0	4.0
SD	0.68	0.62
Range	1.0 to 5.0	1.0 to 4.0
Database Cutoff Date: 24JAN2023		

Source: KEYNOTE-091 EPAR EMEA/H/C/003820/II/0121. [5]

B.2.6.3. Follow-up duration

The median duration of follow-up (defined as the time from randomization to the date of death or the database cut-off date if the participant is still alive) for participants in the Prior Adjuvant Chemotherapy Population was [redacted] months in the pembrolizumab group and [redacted] months in the placebo group (Table 16).

Table 16. Participant Follow-up Duration - Prior Adjuvant Chemotherapy Population (ITT Population)

	Pembrolizumab	Placebo	Total
Participants in population	506	504	1,010
Theoretical Follow-up Duration (Months)[a]			
Participants with data	506	504	1,010
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Actual Follow-up Duration (Months)[b]			
Participants with data	506	504	1,010
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

a: Defined as the time from randomization to the database cutoff date for all participants.
b: Defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive.
Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report. (66)

B.2.6.4. Primary outcome: Disease-free survival (DFS)

At IA3 in the overall population treatment with pembrolizumab continued to demonstrate a clinically meaningful improvement in DFS compared to placebo (median 53.8 months vs 43.0 months; HR: 0.81 [95% CI: 0.68, 0.96]). These results are consistent with those observed in the overall population at IA2 where KEYNOTE-091 met one of the co-primary endpoints and demonstrated statistical significance (median 53.6 months vs 42.0 months; HR: 0.76 [95% CI: 0.63, 0.91]; p=0.00143). (5)

In the PD-L1 TPS <50% subpopulation, the IA3 results demonstrated a clinically meaningful benefit associated with pembrolizumab, with median DFS approximately 17 months longer in the pembrolizumab group compared with the placebo group (51.7 vs 34.5 months). Overall, 168 (46.3%) and 199 (54.8%) DFS events have occurred in the pembrolizumab group and placebo group, respectively, corresponding to 28% reduction in the risk of disease

recurrence or death in the pembrolizumab group compared to the placebo group (HR: 0.72 [95% CI: 0.58, 0.89]) (Table 17).

The DFS Kaplan-Meier curves separated at approximately Month 6 and remained separated through the period assessed (Figure 5), the pembrolizumab group having a higher DFS rates than in the placebo group over time (

Table 18). As a number of participants are still being followed and that the numbers at risk reduce beyond month 60, the tail of the KM curve should be interpreted with caution.

Consistent DFS improvement was also observed in the licensed population (Prior Adjuvant Chemotherapy Population) (median 53.8 months vs 40.5 months; HR: 0.76 [95% CI: 0.64, 0.91]) (

Table 19).

Table 17. Analysis of Disease-Free Survival – PD-L1 TPS < 50% Subpopulation (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median DFS[a] (Months) (95% CI)	DFS Rate at Month 12 in %[a] (95% CI)	vs. Placebo	
							Hazard Ratio[b] (95% CI)[b]	p-Value[c]
Pembrolizumab	363	168 (46.3)	11254.7	1.5	51.7 (39.0, 70.4)	78.3 (73.5, 82.3)	0.72 (0.58, 0.89)	0.00096
Placebo	363	199 (54.8)	10027.2	2.0	34.5 (23.3, 46.4)	69.3 (64.3, 73.8)	---	---

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

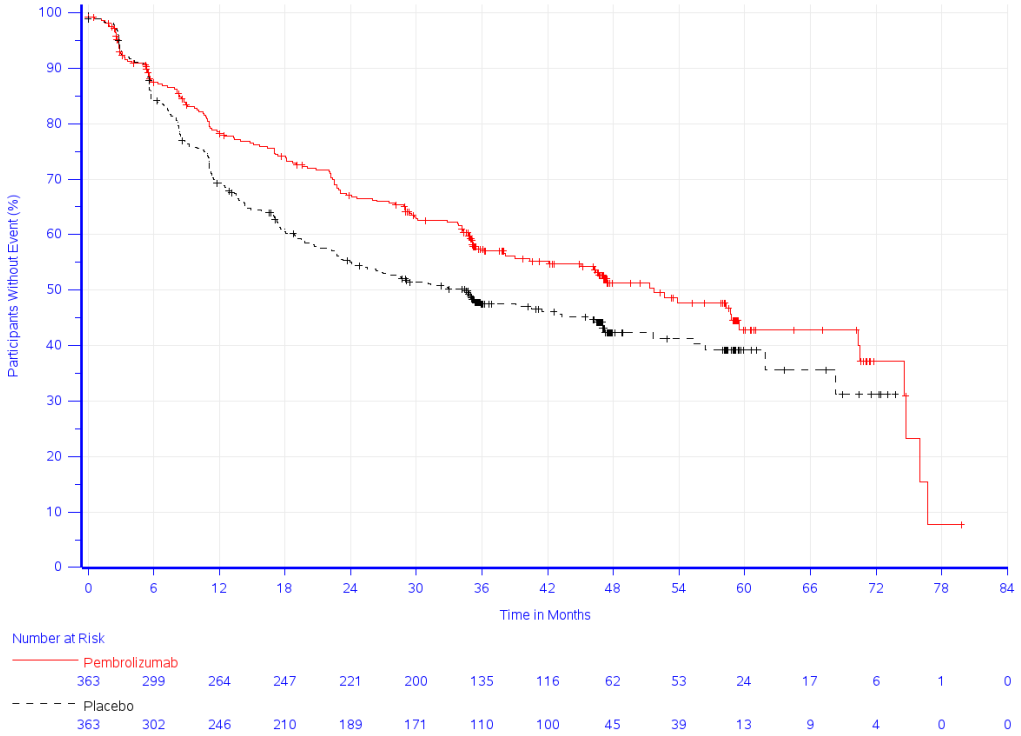
[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[c] One-sided p-value based on the Wald Test in the multivariate Cox regression model.

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report. (66)

Figure 5. Kaplan-Meier Estimates of Disease-Free Survival – PD-L1 TPS < 50% Subpopulation (ITT Population)



Study: KEYNOTE 091 (Database Cutoff Date: 24JAN2023)
Disease-Free Survival (Primary Censoring Rule)
Source: Data on File. KEYNOTE-091 IA3 Statistical Report.[66]

Table 18. Summary of DFS Rate Over Time – PD-L1 TPS < 50% Subpopulation (ITT Population)

	Pembrolizumab (N=363)	**Placebo (N=363)**
DFS rate at 12 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 18 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 24 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 30 Months in (95% CI)[a]	[redacted]	[redacted]

DFS rate at 36 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 42 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 48 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 54 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 60 Months in (95% CI)[a]	[redacted]	[redacted]

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

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report. (66)

Table 19. Analysis of Disease-Free Survival – Prior Adjuvant Chemotherapy Population (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median DFS[a] (Months) (95% CI)	DFS Rate at Month 12 in %[a] (95% CI)	vs. Placebo	
							Hazard Ratio[b] (95% CI)[b]	p-Value[c]
Pembrolizumab	506	225 (44.5)	15754.5	1.4	53.8 (46.2, 70.4)	78.7 (74.8, 82.1)	0.76 (0.64, 0.91)	0.00150
Placebo	504	262 (52.0)	14614.8	1.8	40.5 (32.9, 47.4)	71.0 (66.8, 74.7)	---	---

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

[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[c] One-sided p-value based on the Wald Test in the multivariate Cox regression model.

Database Cutoff Date: 24JAN2023

Source: KEYNOTE-091 EPAR EMEA/H/C/003820/II/0121.(5)

[redacted]

The most common type of first DFS event in both groups was recurrence. Overall, fewer participants in the pembrolizumab group experienced disease recurrence compared with the placebo group (Table 20). The most frequent type of recurrence was distant metastases, which occurred less frequently in the pembrolizumab group ([redacted]%] participants) compared with the placebo group ([redacted]%] participants). The percentage of patients with local and/or regional recurrence was lower in the pembrolizumab group compared to the placebo group ([redacted]%] vs [redacted]%]) (Table 20).

Table 20. Disease Status – PD-L1 TPS < 50% Subpopulation (ITT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	363		363	
Type of First Event in DFS Analysis				
No event	195	(53.7)	164	(45.2)
Event	168	(46.3)	199	(54.8)
Not disease-free at baseline	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Local and/or regional recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Distant metastasis	[redacted]	[redacted]	[redacted]	[redacted]
Both	[redacted]	[redacted]	[redacted]	[redacted]
New malignancy	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
New malignancy includes the second primary and second malignancies. Database Cutoff Date: 24JAN2023				

Source: Data on File. KEYNOTE-091 IA3 Statistical Report. [66]

B.2.6.5. Secondary outcomes: Overall survival (OS)

As DFS was statistically significant in the overall study population at IA2, OS in the overall study population and in participants with PD-L1 TPS ≥50% were formally tested at IA3.

As of the database cut-off date for IA3, a total of 290 OS events were observed in the overall population. The analysis continued to show a trend towards improvement in the OS HR that favoured pembrolizumab over placebo. However, due to the relative early time of the analysis with respect to the OS endpoint (information fraction of approximately [redacted]), the observed p-value did not cross the multiplicity-adjusted, 1-sided p-value boundary at IA3 (HR: 0.87 [95% CI: 0.69, 1.10]; p=0.11792).

In the PD-L1 TPS <50% subpopulation, 84 (23.1%) and 110 (30.3%) OS events were observed in the pembrolizumab and placebo group, respectively, corresponding to HR of 0.73 [95% CI: 0.55, 0.97] (Table 21).

The median OS was not reached for either treatment group confirming the immaturity of OS data at IA3 (Figure 6). The observed OS rate over time is presented in Table 22.

Results in the licensed population (Prior Adjuvant Chemotherapy Population) showed a consistent trend, with median not reached for either treatment group (HR: 0.79 [95% CI: 0.62, 1.01]) (Table 23).

Table 21. Analysis of Overall Survival – PD-L1 TPS <50% Subpopulation (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS[a] (Months) (95% CI)	OS Rate at Month 12 in %[a] (95% CI)	vs. Placebo	
							Hazard Ratio[b] (95% CI)[b]	p-Value[c]
Pembrolizumab	363	84 (23.1)	16271.7	0.5	Not Reached (., .)	95.2 (92.5, 97.0)	0.73 (0.55, 0.97)	0.01626
Placebo	363	110 (30.3)	15782.4	0.7	Not Reached (., .)	94.7 (91.9, 96.6)	---	---

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

[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[c] One-sided p-value based on the Wald Test in the multivariate Cox regression model.

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report. (66)

Figure 6. Kaplan-Meier Estimates of Overall Survival – PD-L1 TPS <50% Subpopulation (ITT Population)

[redacted]

Source: Data on File. KEYNOTE-091 IA3 Statistical Report. [66]

Table 22. Summary of Overall Survival Rate Over Time - PD-L1 TPS <50% Subpopulation (ITT Population)

	Pembrolizumab (N=363)	**Placebo (N=363)**
OS rate at 12 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 18 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 24 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 30 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 36 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 42 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 48 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 54 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 60 Months in (95% CI)[a]	[redacted]	[redacted]
[a] From the product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 24JAN2023		

Source: Data on File. KEYNOTE-091 IA3 Statistical Report. [66]

Table 23. Analysis of Overall Survival – Prior Adjuvant Chemotherapy Population (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS[a] (Months) (95% CI)	OS Rate at Month 12 in %[a] (95% CI)	vs. Placebo	
							Hazard Ratio[b] (95% CI)[b]	p-Value[c]
Pembrolizumab	506	113 (22.3)	22810.0	0.5	Not Reached (., .)	95.6 (93.4, 97.1)	0.79 (0.62, 1.01)	0.03224
Placebo	504	138 (27.4)	22313.1	0.6	Not Reached (., .)	95.0 (92.7, 96.6)	---	---

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

[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[c] One-sided p-value based on the Wald Test in the multivariate Cox regression model.

Database Cutoff Date: 24JAN2023

Source: KEYNOTE-091 EPAR EMEA/H/C/003820/II/0121.[5]

B.2.6.6. Patient Reported Outcomes

Week 48 was selected as the primary timepoint for the mean change from baseline analysis. Results from EORTC QLQ-C30 are presented for the Prior Adjuvant Chemotherapy population according to the approved label. Results from EQ-5D are presented for the PD-L1 TPS <50% subpopulation.

EORTC QLQ-C30 Global Health Status/Quality of Life and supportive PRO analyses

Analyses of global health status/quality of life score of the EORTC QLQ-C30 were prespecified key exploratory PRO endpoints in the overall population.

Based on these early results, global health status/quality of life and scores were stable over time in both the pembrolizumab and placebo groups in the Prior Adjuvant Chemotherapy population with no clinically meaningful differences between the treatment groups. Detailed results are presented in Appendix M.

EQ-5D

Compliance rates for the EQ-5D at baseline through Week 48 were high and similar between the treatment groups (85.9% and 88.7% at Week 48 in the pembrolizumab and placebo group, respectively). At Week 48, the completion rates were 77.0% and 83.0% in the pembrolizumab and placebo group, respectively.

EQ-5D VAS

Analysis of the EQ-5D-5L visual analogue scale (VAS) score at Week 48 showed no clinically meaningful changes from baseline in either treatment groups (Table 24).[69] The difference in least squares (LS) means of the EQ-5D VAS Score at Week 48 was [redacted][95% CI: [redacted] nominal p=[redacted]). The empirical mean change form baseline remained stable over time (Figure 7).

Table 24. Analysis of Change from Baseline in EQ-5D VAS to Week 48 – PD-L1 TPS <50% (PRO FAS Population)

	Baseline		Week 48		Change from Baseline to Week 48		
Treatment	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**LS Mean (95% CI)†**	
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pairwise Comparison						Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab vs. Placebo						[redacted]	[redacted]

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western

Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous) and smoking status (never vs. former/current).

For baseline and Week 48, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report. [66]

Figure 7. Empirical Mean Change from Baseline and 95% CI for the EQ-5D VAS Over Time by Treatment Group (Observed Data Only) – PD-L1 TPS < 50% Subpopulation (PRO FAS Population)

[redacted]

Source: Data on File. KEYNOTE-091 IA3 Statistical Report. [66]

EQ-5D-3L Utility Scores

The EQ-5D utility scores in this submission are calculated using the UK EQ-5D-3L algorithm and value set.

Analysis of the EQ-5D-3L utility score at Week 48 showed no clinically meaningful changes from baseline in either treatment groups (Table 25).[69] The difference in LS means of the EQ-5D-3L Utility Score at Week 48 was [redacted](95% CI[redacted]; nominal p=[redacted]).

Table 25. Analysis of Change from Baseline in EQ-5D-3L Utility Score to Week 48 Based on the United Kingdom Algorithm – PD-L1 TPS < 50% Subpopulation (PRO FAS Population)

	Baseline		Week 48		Change from Baseline to Week 48		
Treatment	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**LS Mean (95% CI)†**	
Pembrolizumab	[redacted]						
Placebo	[redacted]						
Pairwise Comparison					Difference in LS Means† (95% CI)		p-Value†
Pembrolizumab vs. Placebo					[redacted]		[redacted]

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous) and smoking status (never vs. former/current).

For baseline and Week 48, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report. [66]

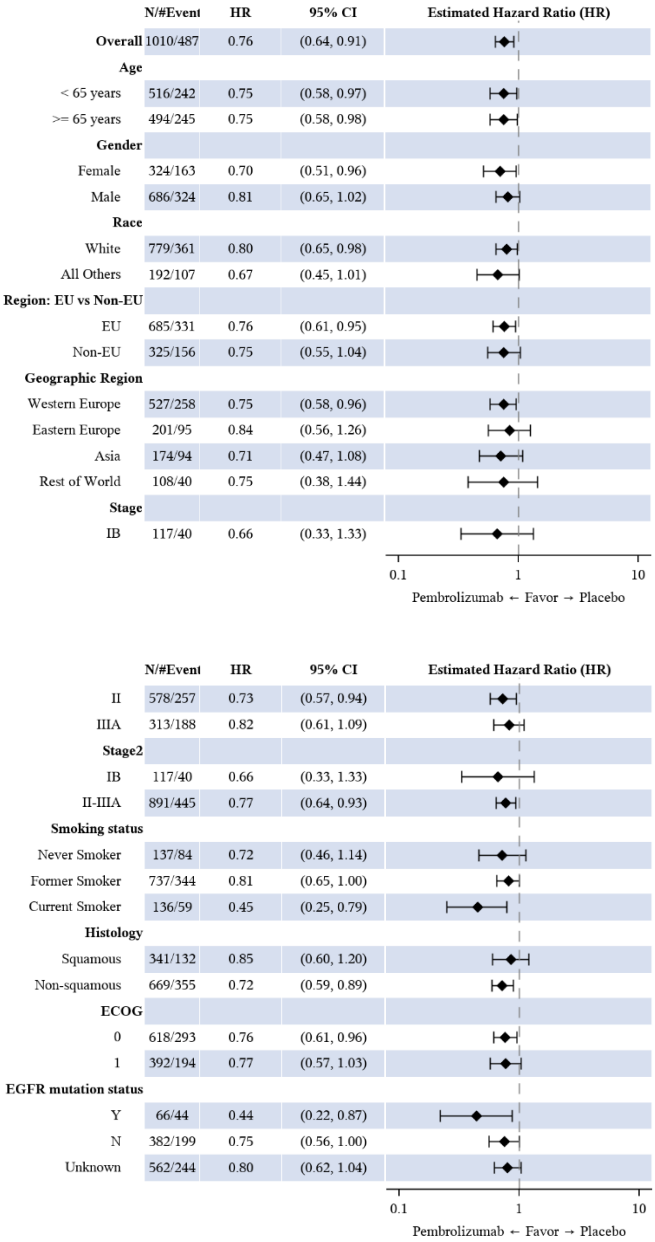
B.2.7. Subgroup analysis

Subgroup analyses were planned to compare DFS and OS by treatment arm in the stratification factors and additional demographic variables as follows:

- Age (< 65 vs. ≥ 65)
- Sex (Male vs. Female)
- Race (White vs. All Others)
- Region (EU vs. Non-EU)
- Region (Western Europe vs. Eastern Europe vs. Rest of the World vs. Asia) – stratification factor
- Stage (IB vs. II vs. IIIA) – stratification factor
- Adjuvant Chemotherapy (No vs. Yes) – stratification factor
- Smoking Status (Never Smoker vs. Former Smoker vs. Current Smoker)
- Histology (Squamous vs. Non-squamous)
- ECOG Performance Status (0 vs. 1)
- EGFR Mutation Status (N vs. Y vs. Unknown)
- PD-L1 Status – stratification factor
    - TPS < 1% vs. TPS = 1-49% vs. TPS ≥ 50%
    - TPS < 1% vs. TPS ≥ 1%
    - TPS < 1% vs. TPS ≥ 50%

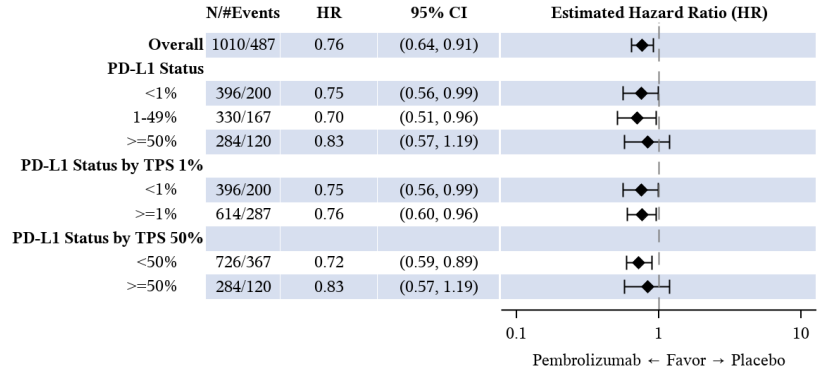
In the Prior Adjuvant Chemotherapy Population (the licensed population) the DFS benefit of pembrolizumab over placebo was consistent across the majority of prespecified subgroups (Figure 8-Figure 9). Some subgroups had a small sample size, which resulted in a wider confidence interval. Further subgroup analysis is not provided for the subpopulation in which reimbursement is sought (PD-L1 TPS <50%) as the small sample size of the subgroups would result in wider confidence intervals and no meaningful conclusions could be drawn about the treatment effect in these subgroups.

Figure 8. Forest Plot of DFS Hazard Ratio by Non-PD-L1 Subgroup Factors - Prior Adjuvant Chemotherapy Subpopulation (ITT Population)



Study: KEYNOTE 091 (Database Cutoff Date: 24JAN2023)
1. For overall population and all subgroups, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (>=50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current). For subgroups, analysis is based on Cox regression model with treatment as a covariate.
2. If a subgroup variable has two levels and one level of the subgroup meets any criteria below, then this subgroup variable will not be displayed: (1) if the number of participants in a category of a subgroup variable is less than 50, (2) the number of events in a category of a subgroup variable is zero in one treatment arm, (3) the number of events in a category of a subgroup variable is less than 5 in the pooled arms.
Source: Data on File. KEYNOTE-091 IA3 Statistical Report. [66]

Figure 9. Forest Plot of DFS Hazard Ratio by PD-L1 Subgroup Factors - Prior Adjuvant Chemotherapy Population (ITT Population)



Study: KEYNOTE 091 (Database Cutoff Date: 24JAN2023)
Note: For overall population and the PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (>=50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).
Source: Data on File. KEYNOTE-091 IA3 Statistical Report. [66]

B.2.8. Meta-analysis

As the SLR identified a single study (KEYNOTE-091 trial) that provided evidence on the clinical effectiveness of pembrolizumab in the patient population relevant to this appraisal, no meta-analysis was performed.

B.2.9. Indirect and mixed treatment comparisons

As the KEYNOTE-091 trial provides robust, head-to-head comparison with the comparator of interest for this appraisal (i.e., active monitoring), no indirect or mixed treatment comparisons were conducted.

B.2.9.1. Uncertainties in the indirect and mixed treatment comparisons

Not applicable

B.2.10. Adverse reactions

Summary of adverse events information

- The Adverse Event (AE) summary profile observed for participants treated with pembrolizumab was generally consistent with the well-known safety profile of pembrolizumab.

- As expected for the comparison of active treatment versus placebo, the frequencies of most AE summary categories were higher in participants treated with pembrolizumab compared with placebo (Table 28). The overall percentage of participants with AEs was similar in the pembrolizumab group compared with the placebo group. The majority of AEs were Grade 1 or 2.
- No new immune-mediated AEs were identified for pembrolizumab in the adjuvant setting. The most frequently reported AEOSIs in the pembrolizumab group for the overall population were hypothyroidism (20.7%), hyperthyroidism (10.7%), and pneumonitis (6.9%).
- Overall, there were 17 deaths due to AEs during the SAE reporting period: 11 in the pembrolizumab group and 6 in the placebo group (Table 32).
- The median drug exposure was similar in both groups (Table 26).

B.2.10.1. Extent of exposure

The median duration on therapy and the median number of administrations was similar in both groups (Table 26). Fewer participants in the pembrolizumab group completed ≥12 months of treatment compared with the placebo group (Table 27).

Table 26. Summary of Drug Exposure - Prior Adjuvant Chemotherapy Population (APaT Population)

	Pembrolizumab (N=496)	Placebo (N=499)	Total (N=995)
Duration on Therapy (days)			
n	496	499	995
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of Cycles			
n	496	499	995
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 24JAN2023			

Abbreviations: APaT: All Patients as treated; SD: standard deviation. Source: Data on File. KEYNOTE-091 IA3 Statistical Report.[66]

Table 27. Exposure by Duration - Prior Adjuvant Chemotherapy Population (APaT Population)

	Pembrolizumab (N=496)			Placebo (N=499)		
	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure						
> 0 m	496	(100.0)	360.4	499	(100.0)	415.4
≥ 1 m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 6 m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Each participant is counted once on each applicable duration category row.
Duration of exposure is the time from the first dose date to the last dose date.
1 Month = 30.4367 days
Database Cutoff Date: 24JAN2023

Abbreviations: APaT: All Patients as treated.
Source: Data on File. KEYNOTE-091 IA3 Statistical Report.[66]

B.2.10.2. Adverse event summary

Adverse events observed as of IA3 (data cut-off date of 24-JAN-2023) are presented in this section for the Prior Adjuvant Chemotherapy population (adverse event summary and AEOSI summary), in line with the approved label, and for the Overall Population (any other AE tables). No substantial differences in the safety profile are expected between the two populations. A consistent safety profile is also expected for the PD-L1 TPS <50% subpopulation. Further details of AEs, including publicly available adverse events data observed as of IA2, are available in Appendix F.

As expected for the comparison of active treatment versus placebo, the frequencies of most AE summary categories were higher in participants treated with pembrolizumab compared with placebo (Table 28).

Table 28. Adverse Event Summary - Prior Adjuvant Chemotherapy Population (APaT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	496		499	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related[a] adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]

[a] Determined by the investigator to be related to the drug.

Non-serious adverse events up to 30 days of last dose, serious adverse events up to 90 days of last dose and Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

NCI CTCAE version 4.03.

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report.[66]

B.2.10.3. Most frequently reported adverse events

The overall percentage of participants with AEs was similar in the pembrolizumab group compared with the placebo group. The most frequently reported AEs (incidence ≥20% in one or both treatment groups) were weight increased, pruritus and hypothyroidism (Table 29). The majority of AEs were Grade 1 or 2.

Table 29. Participants With Adverse Events by Decreasing Incidence (Incidence ≥ 10% in One or More Treatment Groups) – Overall Population (APaT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	580		581	
with one or more adverse events	556	(95.9)	529	(91.0)
with no adverse events	24	(4.1)	52	(9.0)
Weight increased	132	(22.8)	168	(28.9)
Pruritus	125	(21.6)	74	(12.7)
Hypothyroidism	120	(20.7)	27	(4.6)
Arthralgia	107	(18.4)	72	(12.4)
Diarrhoea	106	(18.3)	83	(14.3)
Fatigue	96	(16.6)	89	(15.3)
Cough	87	(15.0)	98	(16.9)
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]

Every participant is counted a single time for each applicable specific adverse event.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose, serious adverse events up to 90 days of last dose and Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Clinical Study Report. [65]

B.2.10.4. Drug-related adverse events

The most frequently reported drug-related AEs (incidence ≥10%) in the pembrolizumab group were hypothyroidism, pruritus, diarrhoea and fatigue (Table 30). The majority of AEs were Grade 1 or 2.

Table 30. Participants With Drug-Related Adverse Events by Decreasing Incidence (Incidence ≥ 5% in One or More Treatment Groups) – Overall Population (APaT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	580		581	

with one or more adverse events	436	(75.2)	305	(52.5)
with no adverse events	144	(24.8)	276	(47.5)
Hypothyroidism	[redacted]			
Pruritus	[redacted]			
Diarrhoea	[redacted]			
Fatigue	[redacted]			
Hyperthyroidism	[redacted]			
Arthralgia	[redacted]			
Rash maculo-papular	[redacted]			
Rash	[redacted]			
Alanine aminotransferase increased	[redacted]			
Pneumonitis	[redacted]			
Nausea	[redacted]			

Every participant is counted a single time for each applicable specific adverse event.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose, serious adverse events up to 90 days of last dose and Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Clinical Study Report.[65]

B.2.10.5. Grade 3 to 5 adverse events

The overall percentage of participants with Grade 3 to 5 AEs was greater in the pembrolizumab group (34.1%) compared with the placebo group (25.8%). The most frequently reported (≥2% incidence) Grade 3 to 5 AEs in one or both treatment groups were hypertension ([redacted]) and pneumonia ([redacted]) (Table 31). The overall percentage of participants with drug-related Grade 3 to 5 AEs was greater in the pembrolizumab group compared with the placebo group (15.3% vs 4.3%).

Table 31. Participants With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ≥ 1% in One or More Treatment Groups) – Overall Population (APaT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	580		581	
with one or more adverse events	198	(34.1)	150	(25.8)
with no adverse events	382	(65.9)	431	(74.2)
Hypertension	[redacted]			
Pneumonia	[redacted]			
Diarrhoea	[redacted]			
Dyspnoea	[redacted]			
Hyponatraemia	[redacted]			
Pneumonitis	[redacted]			

Weight increased	[redacted]	[redacted]	[redacted]	[redacted]

Every participant is counted a single time for each applicable specific adverse event.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days of last dose, serious adverse events up to 90 days of last dose and Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

NCI CTCAE version 4.03

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Clinical Study Report.[65]

B.2.10.6. Deaths due to adverse events

Seventeen participants died during the protocol-specified SAE reporting period (up to 90 days from the last dose of study intervention), 11 (1.9%) participants in the pembrolizumab group and 6 (1.0%) participants in the placebo group (Table 32). [redacted] of the deaths in the pembrolizumab group and [redacted] of the deaths in the placebo group were due to AEs (myocarditis [redacted], cardiogenic shock [redacted], pneumonia [redacted], septic shock [redacted] and sudden death [redacted]) considered to be drug-related by the investigator.

Table 32. Participants With Adverse Events Resulting in Death by Decreasing Incidence (Incidence > 0% in One or More Treatment Groups)- Overall Population (APaT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	580		581	
with one or more adverse events	11	(1.9)	6	(1.0)
with no adverse events	569	(98.1)	575	(99.0)
Myocarditis	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac death	[redacted]	[redacted]	[redacted]	[redacted]
Cardiogenic shock	[redacted]	[redacted]	[redacted]	[redacted]
Completed suicide	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial ischaemia	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]	[redacted]	[redacted]
Aortic aneurysm rupture	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia bacterial	[redacted]	[redacted]	[redacted]	[redacted]

Post procedural pneumonia	[redacted]	[redacted]	[redacted]	[redacted]

Every participant is counted a single time for each applicable specific adverse event.

Non-serious adverse events up to 30 days of last dose, serious adverse events up to 90 days of last dose and Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.

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

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Clinical Study Report.[65]

B.2.10.7. Other serious adverse events

The most frequently reported serious adverse events (SAEs) (incidence ≥2%) in one or both treatment groups were pneumonia and pneumonitis (Table 33).

Table 33. Participants With Serious Adverse Events up to 90 Days of Last Dose by Decreasing Incidence (Incidence ≥ 1% in One or More Treatment Groups) – Overall Population (APaT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	580		581	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]

Every participant is counted a single time for each applicable specific adverse event.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Serious adverse events up to 90 days of last dose are included.

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

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Clinical Study Report.[65]

B.2.10.8. Adverse events leading to discontinuation of study treatment

The overall percentage of participants with treatment discontinuations due to AEs in the Overall Population was greater in the pembrolizumab group (20%) compared with the placebo group (5.9%). The most frequently reported AEs leading to treatment discontinuation (≥1% participants) in the pembrolizumab group were pneumonitis and diarrhoea. Detailed results are presented in Appendix F.

B.2.10.9. Adverse events resulting in treatment interruption

The overall percentage of participants with treatment interruptions due to AEs was greater in the pembrolizumab group ([redacted]) compared with the placebo group ([redacted]). The most

frequently reported AEs leading to treatment interruption (≥2% participants) in the pembrolizumab group were hypothyroidism, diarrhoea, pneumonitis, and arthralgia. Detailed results are presented in Appendix F.

B.2.10.10. Adverse events of special interest (AEOSI)

In the Prior Adjuvant Chemotherapy Population, the majority of AEOSI in the pembrolizumab group had a maximum toxicity of Grade 1 or 2; [redacted] of pembrolizumab-treated participants experienced AEOSIs of Grade 3 to 5. There were [redacted] fatal AEOSIs reported as myocarditis; both events occurred in the pembrolizumab group (Table 34).

In the Overall Population, the most frequently reported AEOSIs (≥5% participants) in the pembrolizumab group were hypothyroidism (20.7%), hyperthyroidism (10.7%), and pneumonitis (6.9%). The Grade 3 to 5 AEOSIs that occurred in ≥1% of participants in the pembrolizumab group were severe skin reactions ([redacted]), hepatitis ([redacted]), and pneumonitis ([redacted]). This was generally consistent with the known safety profile of pembrolizumab.

Table 34. Adverse Event Summary AEOSI Including All Risk Categories - Prior Adjuvant Chemotherapy Population (APaT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	496		499	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related[a] adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]

[a] Determined by the investigator to be related to the drug.
Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included.
NCI CTCAE version 4.03.
Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report.[66]

B.2.11. Ongoing studies

KEYNOTE-091 is an ongoing RCT which is planned to continue until OS events reach the target number required for the final analysis to be conducted. At IA3, 290 and 67 OS events have been reported in the overall population and in the PD-L1 strong positive subgroup, respectively, representing [redacted] and [redacted] of the number of events needed for final analysis. The final analysis of OS will take place when [redacted] and [redacted] events in the overall population and in the PD-L1 strong positive subgroup, respectively, are observed.

However, final OS analysis is planned for approximately [redacted], with one additional interim analysis planned between IA3 and FA OS. As the analyses are event-driven, timelines are subject to change. Given the adjuvant setting, a slow accrual rate of OS events is expected.

B.2.12. Interpretation of clinical effectiveness and safety evidence

The KEYNOTE-091 trial has evaluated the treatment effect of adjuvant pembrolizumab in patients with AJCC v7 stage IB (T ≥ 4 cm)-IIIA NSCLC following complete resection with or without adjuvant chemotherapy.

For those patients that are not eligible for, or choose not to undergo neoadjuvant treatments, the radical treatment of choice remains surgery followed by, in some cases, adjuvant chemotherapy. Despite the curative intent of surgery, these patients face a substantial risk of recurrence with most patients' disease expected to recur within 5 years.[31]

While the Marketing Authorisation covers the early-stage NSCLC population who are at high risk of recurrence following complete resection and platinum-based chemotherapy irrespective of PD-L1 expression, the subpopulation with PD-L1 TPS <50% has a higher unmet need as no adjuvant treatments other than chemotherapy are available for this group.

Consistently with the IA3 results in the overall population (median follow-up: 46.7 months), in the PD-L1 TPS <50% subpopulation treatment with pembrolizumab resulted in 28% reduction in the risk of disease recurrence or death in the pembrolizumab group compared to placebo, with a longer median DFS in the pembrolizumab group compared to the placebo group (51.7 months vs 34.5 months). A lower number of recurrences was reported in the pembrolizumab group ([redacted]% vs [redacted]%) with distant metastasis occurring more frequently in the placebo group ([redacted]%) compared to the pembrolizumab group ([redacted]%).

While a limited number of OS events have occurred in the PD-L1 TPS <50% subpopulation (194/726), the results are suggestive of survival benefit that favoured patients treated with pembrolizumab to placebo (HR: 0.73 [95% CI: 0.55, 0.97]). It is acknowledged that the full magnitude of the overall survival benefit is still uncertain; however, it is unlikely that current

uncertainties will be completely resolved in a timely fashion due to slow accrual of events in the adjuvant setting. One additional interim analysis is planned before the number of events reaches the target number that will allow final OS analysis, which is not expected to occur until [redacted].

Nevertheless, the significant improvement in DFS outcomes can positively impact early-stage resected NSCLC patients as a reduced risk of disease recurrence will likely result in a lower probability for patients to progress to cancer stages where no curative treatments options are available and survival outcomes are poor. Therefore, DFS is a clinically relevant endpoint for early-stage NSCLC patients. This was also confirmed by the Evidence Assessment Group (EAG) and clinical experts during the appraisal of osimertinib as adjuvant treatment for EGFR mutation-positive NSCLC patients.[3]

Additional evidence has shown that intermediate endpoints, such as DFS, can be good predictors for long-term survival outcomes in adjuvant setting for resected early-stage NSCLC:

- Mauguen et al. (2013) assessed the correlations between intermediate endpoints and OS using 2 meta-analyses of adjuvant chemotherapy in NSCLC, involving 7,626 patients in 24 RCTs. The analysis showed correlations between DFS and OS were "very good" at the individual patient level (ρ^2 = 0.83 [95% CI: 0.83-0.83] in trials without radiotherapy) and "excellent" at the trial level (R^2 = 0.92 [95% CI: 0.88-0.95] in trials without radiotherapy);[70]
- In a retrospective observational study using data from the SEER-Medicare database in 1,761 patients (1,182 with recurrence and 579 without recurrence) with newly diagnosed early-stage NSCLC (stage IB, tumour size ≥ 4 cm to stage IIIA; AJCC 7th edition), West et al. (2023) found that over a median of 55.0 months of follow-up, patients with recurrence had significantly shorter OS than patients without recurrence (33.5 vs. 108.4 months; Cox-adjusted HR=3.72 [95% CI: 3.11-4.45]; p< 0.001).[71]

DFS may not be the only mechanism through which patients benefit from immunotherapies like pembrolizumab and experience better response to downstream treatments. Data from KEYNOTE-091 in participants that experienced distant metastasis showed that a numerically lower proportion ([redacted]%) of participants in the pembrolizumab group had brain metastasis compared to placebo group ([redacted]%) (Table 45), which may be indicative of a residual treatment effect of pembrolizumab at later stage.

While further data collection in patients experiencing recurrences would be needed to validate these observations (no imaging data were collected in the trial once participants had

a recurrence), currently available data suggest the possibility of better survival outcomes for patients with loco-regional or metastatic disease previously treated with adjuvant pembrolizumab compared to active monitoring. Potential factors are discussed in section B.3.3.2.

No new safety concerns were identified for pembrolizumab in the KEYNOTE-091 trial. The long exposure combined with the overall incidence of AEs, discontinuations due to AEs, and fatal events suggest pembrolizumab in the adjuvant setting had an acceptable tolerability. As expected for the comparison of active treatment versus a medically inert treatment such as placebo, the frequencies of most AE summary categories were higher in participants treated with pembrolizumab compared with placebo. However, the majority of AEs were Grade 1 or 2 and no new immune-mediated AEs were identified for pembrolizumab.

Internal validity

- KEYNOTE-091 is a randomised triple-blinded trial that has evaluated the effects of pembrolizumab versus placebo, which allows an unbiased evaluation whilst using a comparator that reflects current clinical practice.
- While the DFS and OS analysis presented in the PD-L1 TPS <50% subpopulation have not been formally tested, they accounted for relevant adjusting factors based on multivariate Cox regression model. The sample size was sufficiently large to have likely detected a difference in DFS between the two treatment groups.
- However, the sample size of the subgroups within the subpopulation of interest is overall small and therefore the subgroup analysis would fail to generate any robust evidence about the treatment effect in these subgroups.

External validity

The results of the KEYNOTE-091 trial can be considered generalizable to the clinical practice in the UK. The outcomes evaluated in the trial are in line with the NICE scope as relevant to both patients and clinicians.
Also, the trial population broadly reflects the characteristics of the population in the UK, which further supports the generalisability of the evidence and its relevance to the decision problem.

Both trial arms underwent regular disease evaluation (active monitoring). Effectively, the comparator arm (placebo group) received active monitoring as the only ‘active’ treatment and therefore it is a relevant comparator in this appraisal as reflecting current clinical practice in the UK.

Limitations include currently available data having failed to show beneficial effects across PD-L1 subgroups, with some uncertainties in the PD-L1 strong positive (PD-L1 TPS ≥50%) still remaining, which is likely to be due to overperforming control arm. This contradicts clinical expectations, given the known positive predictive value of PD-L1 expression and the outcomes of pembrolizumab in the metastatic setting (e.g., KEYNOTE-024[62], KEYNOTE-189[60], KEYNOTE-407[61] and KEYNOTE-001[72]) as well as other immunotherapies in the adjuvant setting. While the true difference between pembrolizumab and placebo is likely to be observed with more mature data, pembrolizumab is unlikely to be the preferred option in clinical practice for the PD-L1>50% group.

Based on the above, and considering the observed beneficial effects for the PD-L1 TPS <50% patients, this submission is aiming to address the subpopulation in the adjuvant setting with a substantial unmet need whose clinical benefits associated with pembrolizumab are supported by robust evidence.

Pembrolizumab would represent a ‘step-change’ in the management of the condition for this patient group by improving the probability that their radical treatment plan is genuinely curative.

B.3. Cost-effectiveness

Summary of key cost-effectiveness information

Objective:

- To model the cost-effectiveness of pembrolizumab as adjuvant treatment up to one year/18 cycles for patients with PD-L1 TPS<50% and fully resected NSCLC, following successful completion of adjuvant chemotherapy.

Model structure:

- There is no standard model structure in early NSCLC. A Markov model with 4 health states was developed. This was a more transparent and parsimonious model structure than others we reviewed that still captured the main elements of the clinical pathway and disease course. Comparisons with previous models submitted to NICE are discussed.

Model inputs:

Patient population inputs:

- Patients with PD-L1 TPS<50% and fully resected NSCLC following successful completion of adjuvant chemotherapy.

Clinical efficacy inputs:

- Transition probabilities from the Disease-Free health state, adverse events and most utility data are taken from the KEYNOTE-091 trial.
- Transitions from the Local-regional Recurrence state are taken from real-world evidence sources.
- Transitions from the Distant Metastases state are taken from published trials for downstream treatments.
- Transitions have some time-limited calibration added to match observed Overall Survival from the trial.

Utility inputs:

- Utility for adverse events and for the Disease Free and Local-regional Recurrence health states was measured in the KEYNOTE-091.
- Utility for the Distant Metastatic state was derived from Progression Free and Progressed Disease utility data in pivotal metastatic trials.

Costs and resource use inputs:

- Resource uses associated with downstream treatments and general management of the condition were elicited at UK advisory boards.
- Unit costs were sourced from NHS reference costs or other standard UK cost databases

Base-case results and sensitivity analyses:

- The base-case and most key scenarios were within a range of £20-£30,000/QALY gained. In no scenarios was the ICER above £30,000/QALY.

Cost-effectiveness conclusions:

- Treatment with pembrolizumab accrues QALYs by increasing the number of years patients spend disease free. In common with other adjuvant treatments, it is expected to increase the proportion of patients who are genuinely cured by their radical treatment plan. The initial costs are offset to some degree by a reduction in the need for downstream care.
- ICERs were within the range of £20-30,000/QALY gained and as such, the model suggests that pembrolizumab is a cost-effective addition to standard care when used in this setting.

B.3.1. Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify published cost-effectiveness studies (CEA) for pembrolizumab and other NSCLC therapies in the adjuvant setting which can be found in Appendix G.

B.3.2. Economic analysis

A de novo economic model was developed to assess the cost-effectiveness of pembrolizumab as an adjuvant treatment for the PD-L1 TPS <50% subpopulation. As stated in Table 1, the comparator in this appraisal is active monitoring. This section will describe the economic model developed in support of this appraisal and the rationale for the model that was developed.

B.3.2.1. Patient population

As stated in Section B.1.1., the patient population considered for this current appraisal is adults with NSCLC who have undergone complete surgical resection after adjuvant chemotherapy and whose tumours have PD-L1 TPS <50%. Whilst this differs to the population specified in the final NICE scope, as explained in Section B.1.1 Table 1, the PD-

L1 TPS <50% subpopulation is considered the patient group within the licensed population with higher unmet need that will benefit more from an additional effective adjuvant treatment.

The starting age and gender distribution of the model cohort in cycle 0 was based on the reported characteristics of the KEYNOTE-091 trial population (N=1,177) as summarised in Table 35. Means and standard errors of body surface area and body weight were also based on KEYNOTE-091. Glomerular filtration rate (GFR) was estimated from a previous NICE appraisal pemetrexed (TA181), which estimated that a target area under the curve (AUC) of 5 would require 500 mg dose of carboplatin on average. [73] Mean GFR was accordingly estimated to be 75 ml/min/1.73m2 based on the dosing equation of 500 = 5(GFR+25). Body surface area, weight, and GFR were used within the model to compute the required dosage of certain subsequent treatment options in the metastatic NSCLC setting.

Table 35. Baseline characteristics of the population used in the cost-effectiveness analysis

Characteristic	Overall	Source
Starting age (years), mean	64.3 years	KEYNOTE-091
Percentage female (percentage)	31.7%	
Body surface area (m^2), mean	1.9	
Body surface area (m^2), standard error	0.01	
Weight (kg), mean	74.8	
Weight (kg), standard error	0.5	
Glomerular filtration rate (GFR) (ml/min/1.73m^2)	75.0	NICE TA181

B.3.2.2. Model structure

Table 36 summarises the key features of the base-case cost-effectiveness analysis along with a comparison with other adjuvant NSCLC models previously considered by NICE.

Table 36. Features of the economic analysis

	Previous NICE evaluations		Current evaluation	
Factor	**Osimertinib (TA761)**	**Atezolizumab (TA823)**	**Chosen values**	**Justification**

Model structure	Markov with five health states (disease free, local-regional recurrence, first-line treatment for DM, second-line treatment for DM, death). Sub-models and tunnel states are used to handle time-dependency in intermediate states.	Markov with five health states (disease free survival, local-regional recurrence, first-line metastatic recurrence, second-line metastatic recurrence, death)	Markov with four health states (disease free, local-regional recurrence, distant metastases and death). Calibration to observed OS in the base-case.	There is no standard approach to modelling adjuvant NSCLC. A variety of structures have been used in the published literature. Further details of the TA761 and TA823 models are summarised in Appendix G but key details related to the features of the economic analysis are included here. In TA761, the company used a Semi-Markov model structure, sub-models and tunnel states to attempt to handle time-dependency in intermediate states. This approach appears to have been highly computationally complex and the EAG identified multiple programming errors during Clarification Questions. The TA823 model was simpler but attracted some criticism for under-fitting to observed OS. A scenario where the observed OS was used directly was then explored. In our *de novo* model, we used the same 4-state Markov structure that has been commonly used in appraisals of adjuvant treatments in other cancers (TA766, TA837 or TA851). In the case of NSCLC, this model also captures the key outcomes from the trial, and the main features of the clinical pathway and patient experience as they would be within the NHS, while adhering to the principles of model parsimony and transparency. [3] [2] Of note, we believe it is reasonable to capture the outcomes in DM using a single OS curve and weighting the costs and outcomes for first and second line treatments within this health state.

Time horizon	37 years	40 years	35.7 years	Lifetime time horizon based on mean age in KEYNOTE-091 of 64.3 years. After 35.7 years, virtually all modelled patients have died and so lifetime costs and benefits are captured in the economic model.
Cycle length	4.35 weeks	1 month	1 week	Weekly cycle length was used to allow for precise calculation of drug acquisition and administration costs based on recommended administration schedules.
Half-cycle correction	Yes	Yes	Yes	A half-cycle correction (HCC) was applied to costs and effectiveness for additional precision. HCC was not applied where cost and utility components that are incurred at the beginning of a cycle e.g., adjuvant drug acquisition and administration costs (recurring costs starting from week 0) and AE-related costs and disutility (applied as a one-time cost at week 0).
Treatment waning effect?	N/R from the Committee Papers	Included in scenario analysis only	Not included. Cure point instead.	The rationale for why no treatment effect waning is applied from the DF health state is given in B.3.3.
Source of utilities	• SF-36 (from ADAURA37) mapped to EQ-5D-3L • EORTC QLQ-C30 (from FLAURA63) mapped to EQ-5D-3L • EQ-5D-3L estimates form literature (Labbé et al[74])	Various sources identified via an SLR: • (Disease-free survival: Yang et al. 2014 [75] • Local-regional recurrence: Chouaid et al 2013[76] (curative), Van den Hout et al. 2006[77] (palliative) 1L	EQ-5D-3L from KEYNOTE-091	Use of the EQ-5D-3L from KEYNOTE-091 is in line with recommendations in NICE methods guide on the EQ-5D.[78]

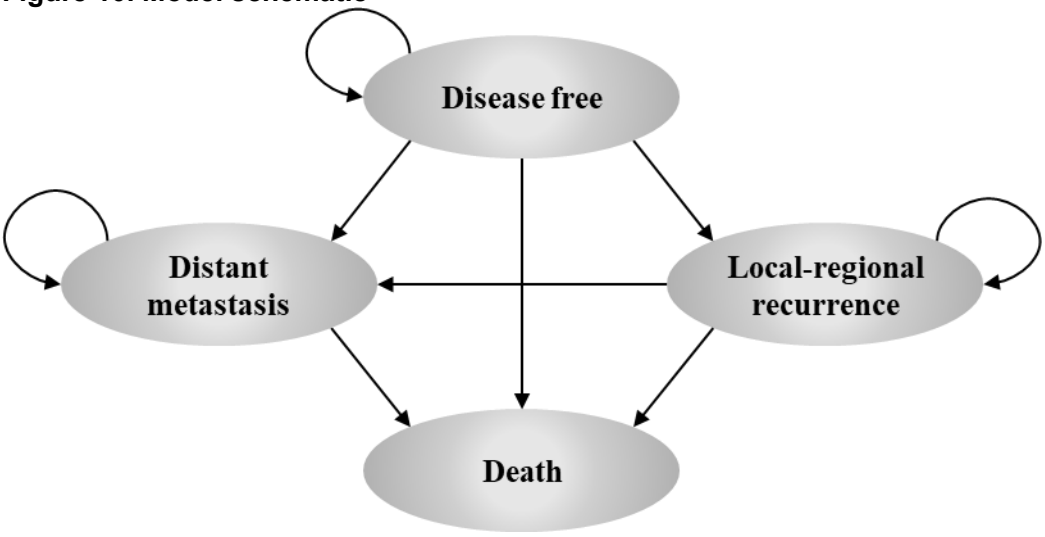
		• metastatic recurrence : IMpower150 2L metastatic recurrence : IMpower150)		
Source of costs	NHS Reference costs (2018/2019), BNF, eMIT	NHS Reference costs (2019/2020), BNF, eMIT	NHS Reference costs (2021/2022), BNF, eMIT	Standard cost databases that reflect the perspective of the NHS and PSS, in line with NICE reference case.
Discount rate	3.5% to costs and effects	3.5% to costs and effects	3.5% to costs and effects	In line with the NICE reference case.

Abbreviations: BNF: British National Formulary, eMIT: electronic market information tool; EQ-5D: EuroQol-5 Dimension; HCC: Half cycle correction; SF-36: 36-Item Short Form; PSS; Personal Social Services

This cost-effectiveness model was developed in Microsoft Excel® using a Markov cohort structure. In contrast to the partitioned survival model structures that are often used to model advanced cancers, Markov models are commonly used for appraisals of adjuvant treatments for earlier-stage cancer indications in which OS cannot be directly modelled using the available pivotal trial data (as seen, for example, in the osimertinib and atezolizumab appraisals, [2, 3] as well as across a range of other pembrolizumab submissions to NICE in other adjuvant indications).[79-82]

The state transition diagram in Figure 10 illustrates the specific health states and allowable transitions in the Markov model. The model consists of four mutually exclusive health states (i.e., disease-free, local-regional recurrence, distant metastases, and death) to track the disease course and survival of patients over time. This model structure differentiates health states by type of recurrence (either local-regional recurrence or distant metastasis) as the primary endpoint of the KEYNOTE-091 trial (DFS) encompasses both types of recurrence events. These two types of recurrence were expected to have different implications on patients' prognosis, health-related quality of life, and disease management, and therefore result in different health outcomes and costs.

Figure 10. Model schematic



Note: Transitions from DF are taken from KEYNOTE-091, transitions from LR are taken from real-world evidence, transitions from DM are taken from various trials. The DM state captures the weighted average of costs and effects across first- and second-line therapy. Transitions from LR and DM are calibrated to trial OS in the base-case.

All patients enter the model in the DF state following surgical resection and adjuvant chemotherapy, with disease stage, and PD-L1 distribution consistent with the KEYNOTE-091 trial patient population at baseline. Adjuvant therapy in the DF health state (i.e.

pembrolizumab or active monitoring) affects patients' risks of transitioning directly from DF to LR, DM, or death. Originally, the model was set up to assume that exposure to pembrolizumab provided no continuing therapeutic/treatment effect once a patient has experienced recurrence (LRR or DM). However, while the model predicted the observed OS in the active monitoring arm of KEYNOTE-091 reasonably well, it significantly underpredicted OS in the pembrolizumab arm. To address this, we added functionality to temporarily calibrate the downstream transition probabilities in the model so that modelled pembrolizumab OS matched observed OS for the observed period. Further discussion of this is included in section B.3.3.1. In KEYNOTE-091, follow-up imaging data was not routinely collected once patients had experienced local-regional recurrence as their first event. This meant it was not possible to obtain LR→DM and, DM→Death and LR→Death transition probabilities, so external data sources were required to estimate these. Patients in the LR state can receive another line of treatment, including chemotherapy and radical treatment (radiotherapy, surgery), and are assumed to receive the same treatments in this setting regardless of model arm.

Once patients transition to the DM state, patients are assumed to receive first and second lines of treatments and the mix of treatments received is influenced by adjuvant therapy received. Risks of transitioning from DM to death are assumed to be driven by the efficacy of the specific first-line treatment received for DM.

B.3.2.3. Intervention technology and comparators

Pembrolizumab was considered in the economic analysis as per the licensed dosing regimen (i.e. administered intravenously at a fixed dose of 200mg every 3 weeks [Q3W]). As per the KEYNOTE-091 trial protocol, patients could receive a maximum 18 cycles (approximately 1 year) of pembrolizumab therapy. As stated in Section B.1.1, the proposed indication for pembrolizumab is the PD-L1 TPS <50% subpopulation.

The NICE final scope specifies 'established clinical management' as the comparator for this patient population, which consists of regular follow-up with clinical visits and scans to monitor disease recurrence. In the context of the current cost-effectiveness analysis, this comparator will be referred to as 'active monitoring'. The outcomes observed in the placebo arm of KEYNOTE-091 were considered representative of the outcomes associated with active monitoring in the UK (i.e. active follow-up and no active or systemic treatment in the adjuvant setting). Other comparators listed in the final NICE scope i.e. platinum doublet chemotherapy and durvalumab (subject to NICE appraisal) were not considered relevant due to the reasons stated in Table 1 in Section B.1.1.

B.3.3. Clinical parameters and variables

All patient level data from KEYNOTE-091 was taken from IA3 (data cut-off date of 24-JAN-2023); the availability of the next KEYNOTE-091 data cut (interim OS) is uncertain as this is event driven but is estimated to be available in [redacted].

B.3.3.1. Overview of transitions and clinical data used in the model

The set of allowable transitions and corresponding data sources are summarised in Table 37. The key transition probabilities driving the cost-effectiveness results are the three transitions starting from the disease-free state (i.e., disease-free to local-regional recurrence, disease-free to distant metastases, and disease-free to death). These transition probabilities were estimated using randomised controlled trial data from KEYNOTE-091 for the pembrolizumab and placebo arms.

Table 37. Baseline summary of transitions and estimation approaches

Transition(s)	Estimation approach	Data source(s)
DF → LR **DF → DM** **DF → Death***	• The pembrolizumab and placebo arms were based on a parametric multistate modelling approach in which different parametric functions were fitted to each of the three individual transitions starting from DF, accounting for competing risks. • A cure assumption was applied among patients who achieve long-term DFS. Specifically, the per-cycle risks of transitions from the disease-free state was gradually reduced by 95% for patients who achieve DFS ≥5.	• Patient-level data from KEYNOTE-091. • UK national life tables were used as minimum transitions to death and as the only DF->Death transition for cured patients.
LR → DM **LR → Death**[1]	• For LR to DM and LR to death: exponential competing risks models were fitted using KM data on equivalent patients in the SEER-Medicare database (SEER data: 2007-2017; associated Medicare claims data: 2007-2019). This was then calibrated to optimise statistical fit between the predicted vs. observed OS in each arm of KEYNOTE-091. The LR to DM and LR to death rates were simultaneously calibrated to each arm of the KEYNOTE-091 trial, by rescaling both rates by the same multiplicative factor and identifying the value of this multiplicative factor that minimised the MSE between	• Patient-level analysis of the SEER-Medicare cohort, matched to patients in KEYNOTE-091 (SEER data: 2007-2017; associated Medicare claims data: 2007-2019). OS Kaplan-Meier curves from KEYNOTE-091. • UK national life tables were used for minimum transitions to death.[1]

	predicted vs. observed OS in each arm. • Rescaled values were returned to observed values from SEER-Medicare after the available follow-up time in KEYNOTE-091 trial.	
DM → Death[1]	• Transition probabilities from DM to death depended upon assumed market shares of first-line treatments for metastatic NSCLC and the efficacy of those first-line treatments with respect to OS. • Market share was affected by assumptions around when patients in the pembrolizumab arm would be eligible for rechallenge with pembrolizumab (only if recurrence occurred >18 months in the base case). • Exponential OS distributions were estimated for each first-line treatment based on trials in metastatic NSCLC. Exponential PFS distributions were similarly estimated for each first-line treatment. PFS is factored into the calculation of utility and disease management costs in the DM state. • Transition probabilities were also calibrated in the short term so that the model predicted observed OS	• OS and PFS results from KEYNOTE-189/407 and other trials in metastatic NSCLC. • Patient-level analysis of the SEER-Medicare database • National life tables - for minimum transitions to death

Abbreviations: CI, confidence interval; DF, disease-free; DM, distant metastases; EMR, electronic medical record; LR or LRR, local-regional recurrence; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; SLR, systematic literature review. [1] Transition probabilities to death were constrained to be at least as high as all-cause mortality, as estimated from UK life tables given the age and gender distribution of the cohort at each cycle.

Modelling transitions from disease-free state

The transition probabilities starting from the disease-free state were estimated based on survival analyses of individual patient-level data from the KEYNOTE-091 trial, following the parametric multistate modelling approach described by Williams et al. (2017a & 2017b). [83, 84] Parametric models were used to estimate the cause-specific hazards of each transition over time within the pembrolizumab and placebo arms of the trial in the PD-L1 TPS <50% population. Within each weekly cycle of the model, the probability of each of these transitions (as well as the composite probability of any DFS failure event) were calculated as a function of all three cause-specific hazards.

Estimation of cause-specific hazards for each individual transition starting from the disease-free state

In order to fit parametric models to each of the three individual health state transitions, standard survival analysis methods were used with one modification to account for competing risks: when analysing time to each specific type of DFS failure, the two competing failure types were treated as censoring events [85, 86]. For example, to model the transition from disease-free to distant metastases, patients who experience a local-regional recurrence or death prior to distant metastases were censored at the time of the earlier competing event. After these additional censoring criteria were applied to the patient-level time-to-event data for each transition, standard parametric curve fitting was performed.

The following parametric modelling approaches were used to explore uncertainty in the estimation of transition probabilities starting from the disease-free state:

- Approach #1: Parametric models separately fitted to each treatment arm: transition probabilities were estimated based on parametric models that were fitted individually to each treatment arm of the KEYNOTE-091 trial. A full suite of parametric functions was considered to model transitions from disease-free to local-regional recurrence and from disease-free to distant metastases in each treatment arm.

- Sensitivity analysis: parametric proportional hazards models with treatment arm variable: Under Approach #2, transition probabilities in the pembrolizumab and placebo arms were estimated based on jointly fitted models that assume proportional hazards (i.e., exponential, Weibull, or Gompertz). The models thus assumed a time-constant hazard ratio (HR) for pembrolizumab versus placebo in KEYNOTE-091. Accelerated Failure Time models were not explored in this sensitivity analysis for computational simplicity and is also consistent with previous pembrolizumab appraisals accepted by NICE (TA766, TA830, TA837).[79, 81, 82]

- Sensitivity analysis: Parametric proportional hazards models with piecewise fittings (before and after year 1): Under Approach #3, the parametric models under Approach #2 incorporated both a treatment arm variable and a time-varying binary indicator equal to 1 in the pembrolizumab arm during the portion of follow-up after 1 year and 0 otherwise. The models thereby estimated a hazard ratio for during and after the first year following initiation of adjuvant therapy (i.e. protocol-defined maximum treatment duration of 1 year). Upon investigation there appears to be limited advantage in this approach but we have included it in the discussion for completeness.

For all three approaches, due to the small numbers of direct transitions from DF to death observed in KEYNOTE-091, exponential distributions were fitted for this transition in each arm. These models had good visual fit and require the fewest parameters and assumptions.

For each of the two model arms, probabilities of each transition from the disease-free state were calculated based on all three cause-specific hazard functions. The predicted DFS curve over time in each treatment arm similarly depended upon all three cause-specific hazard functions. Therefore, to select base-case parametric functions, all 67 (i.e., 7×7 in Approach #1 + 3×3 in Approach #2 + 3×3 in Approach #3) possible combinations of parametric functions for disease-free to local-regional recurrence and disease-free to distant metastases transitions were considered and are summarised in Appendix N for further details.

Calculation of transition probabilities based on cause-specific hazards

For each individual transition starting from the disease-free state, transition probabilities in each weekly cycle were calculated within the model as a function of the cause-specific hazards for all three types of DFS failure. The following calculation steps were performed:

1. For each cause of DFS failure *k* (i.e., local-regional recurrence, distant metastases, or death), the average cause-specific hazard within the cycle from week *(t-1)* to *t* was calculated as:

$$\overline{h}_k(\mathrm{t}) = H_k(\mathrm{t}) - H_k(\mathrm{t}-1),$$

   Where $H_k(.)$ is the cause-specific cumulative hazard of cause *k* (based on the parametric function selected to model cause *k*).

2. The average hazard of any DFS failure within the cycle from week *(t-1)* to *t*, denoted $\overline{h}_{DFS}(\mathrm{t})$, was calculated as the sum of the average cause-specific hazard for all three causes within that cycle. This hazard was converted into a probability using the formula:

$$1 - e^{-\overline{h}_{DFS}(\mathrm{t})}$$

3. In each cycle, the relative contribution of each cause *k* to the overall hazard of DFS failure was derived as:

$$\frac{\overline{h}_k(\mathrm{t})}{\overline{h}_{DFS}(\mathrm{t})}$$

This represents the probability of having had an DFS failure of type *k* given that an DFS failure has occurred within the cycle. [87]. The relative contribution of cause *k* was then multiplied by the probability of any DFS failure within the cycle to obtain the transition probability corresponding to cause *k*.

Within each cycle, the transition probability from disease-free to death was set equal to the maximum of the estimated probability based on parametric modelling and background mortality (based on UK lifetables), given the age and gender distribution of the cohort by that cycle.

Model selection

Patients in the DF state in the KEYNOTE-091 model may exit into one of three health states (LRR, DM or Death) and therefore the proportion of patients remaining DF is determined by a combination of competing risks survival models, rather than by a single survival model. As noted by the NICE DSU TSD 19[85], assessing model fit is more challenging in the context of multistate models than in partitioned survival models for this reason. To select base-case parametric functions for each cause-specific transition, all 67 possible combinations of parametric functions for disease-free to local-regional recurrence, disease-free to distant metastases, and disease-free to death were considered. Consistent with NICE DSU's TSD 14 guidance [88], and in the absence of strong evidence to the contrary, the base-case parametric functions used the same functional form to model each health state transition in both pembrolizumab and placebo arms (e.g. DF→LRR would be log-normal in both arms). The appropriateness of the base-case parametric functions were assessed using the following criteria:-

- Visual assessment of fit vs. observed individual cumulative incidence curves and aggregated DFS: Predictions generated by different combinations of parametric functions were visually assessed against the observed data in each trial arm, following the approach used by William et al. (2017). Specifically, predicted versus observed cumulative incidence curves were plotted for each of the three individual transitions starting from the disease-free state. The resulting predictions of DFS as a composite endpoint were also compared against the observed DFS KM curve in each arm.
- Fit based on weighted mean squared error (MSE) vs. observed DFS: The weighted MSE was used to assess fit of the predicted DFS curve versus the observed KM curve during the within-trial period in each treatment arm. Other fit statistic measures such as Akaike Information Criterion (AIC), are not readily available for composite endpoints comprised of multiple competing risks curves. MSE was calculated based on the

average of the squared difference in predicted versus observed DFS at weekly intervals across the within-trial period, weighted by number of patients at risk in each weekly interval.

- Assessment of modelled OS vs. observed OS in KEYNOTE-091: models were assessed against their relative ability to predict the observed OS within the trial period. All models predicted placebo OS reasonably well but underpredicted OS in the pembrolizumab arm. We rejected models that had the greatest level of underprediction.
- Assessment of clinical plausibility of long-term extrapolations (clinician feedback)

Clinicians at the UK 2023 Clinical Advisory Board confirmed they expected the separation between the DFS KM curves to continue rather than to come together i.e. they expected that adjuvant pembrolizumab would increase the probability that patients would be cured in the long term rather than merely delaying recurrence.[45] They confirmed that they expected the separation in DFS KM curves to translate into roughly the same separation in OS over time. We rejected models that had a trend towards early convergence of DFS and OS.

For the DF->Death transition there were very few events in either arm and all models fit similarly (see Appendix N). We concluded there was no reason to deviate from simple exponential models in both arms for this transition. The selection process for base-case parametric distributions of disease-free to local-regional recurrence and disease-free to distant metastases along with detailed tables and figures is detailed in Appendix N. The steps are summarised here:-

1. All models based on Approaches #2 and #3 had relatively poor visual fit to one or other of the curves as the curves are anchored by a static hazard ratio for most or all of the follow-up time. These were therefore excluded from primary analyses but these were retained for the purposes of scenario analyses.

2. We noted that all curves for DF→LRR in both arms fit reasonably well and are very similar to each other. We concluded that basing curve selection on this transition would be difficult.

3. We noted that using a log-normal curve for the DF→DM transition in the pembrolizumab arm provided the lowest MSE in Approach #1 regardless of what DF->LRR transition it was paired with (positions 1, 4, 6, 7, 9, 13, 16 of the overall MSE table [see Appendix N]). It also provided a very close visual fit to the DF→DM cumulative incidence

curve. We concluded there was relatively strong evidence that curve sets based on log-normal DF→DM transitions in the pembrolizumab arm would provide the best fit.

4. We inspected the cumulative incidence curves for the DF→DM transitions in the placebo arm and noted that the Gompertz model resulted in zero hazards by 5-6 years so we excluded it. The Weibull, log-logistic and gamma curves appeared to first under then over predict the cumulative incidence curves so we excluded them. We noted that the generalised gamma and log-normal curves appeared to fit the data reasonably well.

5. We were mindful of the guidance in TSD14 about using the same model type in both arms unless there is strong evidence to the contrary. We noted that using the log-normal curve for the DF→DM transition in the placebo arm provided MSEs that were in the top half (positions 2, 13, 16, 20, 27, 30, 31). We examined all 7 pairs of curve sets where DF→DM transitions followed the log-normal curves in both arms and excluded the Gompertz/log-normal and generalised gamma/log-normal curves due to early convergence of DFS and OS and more severe underprediction of observed pembrolizumab OS in the trial than the other models.

6. We concluded that log-normal/log-normal curves for both arms based on Approach #1 were the most appropriate based on the following criteria as shown in Figure 11:-

   a. Approaches #2 and #3 provided relatively poor visual fit to DFS compared to Approach #1

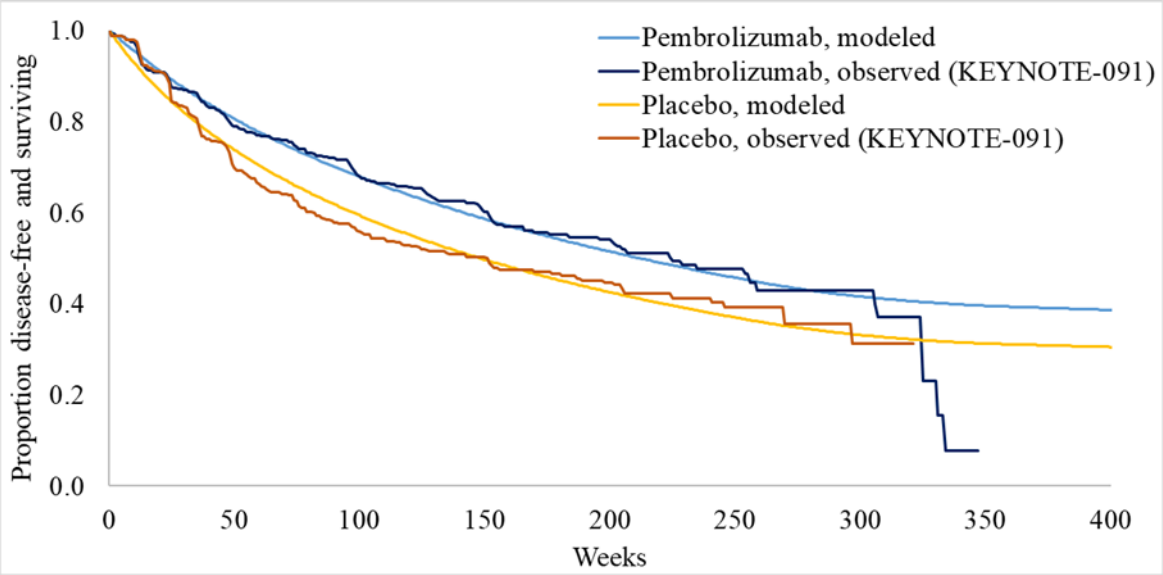
   b. To fit the same model type in both arms as recommended by NICE TSD14 guidance[88] in the absence of strong evidence to the contrary

   c. Log-normal based models for DF->DM being consistently the best fitting to DFS in the pembrolizumab arm and within the top half in the placebo arm and one of only two that fit the DF->DM transition in the placebo arm

   d. Of the 7 log-normal combinations we excluded 2 based on clinical plausibility (much narrower implied OS benefit than observed in the trial and expected by clinicians)

   e. Of the remaining 5 we selected log-normal/log-normal as it had the lowest average MSE across the two arms and because log-normal was a central estimate among the DF->LRR models

Figure 11. Final selected DFS model; DF->LRR (log-normal), DF->DM (log-normal), DF->Death (exponential) for both arms



Cure point

The model allows a cure period to be implemented whereby the per-cycle risk of progression (movement to both LRR and DM) from the disease-free state is reduced by 95%; the risk reduction to 95% is applied with a linear rate during the cure period (i.e. from 0% to 95%). The same risk reduction is applied to the risk of transitions from disease-free to death subject to the constraint that the risk of disease-free to death must always be at least as high as background mortality. This approach' along with a 95% cure proportion was also used in TA761.

The base-case assumes a cure period from 5 to 7 years. This is based in part on feedback from clinical experts from the 2022 Clinical Advisory Board[45], which suggested that it is reasonable to assume there will be very few recurrences or disease-related deaths after 5 years, and that this is reflected in that patients are not routinely followed up in secondary care after this. This is also consistent with the feedback from clinical experts elicited in the atezolizumab submission (TA823) and the osimertinib submission (TA761). In TA761, patients with completely resected early-stage NSCLC are typically discharged from care after 5 years if they have not experienced disease recurrence (and so are subsequently unmonitored).[89] It is also consistent with assumptions the NICE Guideline Committee made during development of NG122. All patients who were in the DFS state at 5 years post radical treatment were assumed cured in the IIIA-N2 model that was built as part of Evidence Review C. However, suddenly imposing a cure point at 5 years resulted in a noticeable visual 'kink' in the DFS curve, so we smoothed this out by linearly increasing the cure proportion between 5-7 years.[45, 46]. To reflect this, disease-free health state monitoring

costs in the model are only accrued for the proportion who are not functionally cured (i.e., during the cure period and post-cure period).

A gradual 5 to 7-year cure period with a 95% cure rate can be considered conservative given the consistent clinical feedback across all adjuvant appraisals; a narrower cure period with 100% risk reduction could be just as plausible, and so was examined in sensitivity analysis.

The assumption is also broadly consistent with the shape of the observed KEYNOTE-091 DFS and OS data - Kaplan Meier curves where declining hazards are observed and plateauing is emergent towards the end of follow-up time, implying that functionally cured patients comprise an increasingly growing proportion of the remaining N at risk.

Treatment effect waning from the disease-free health state

No treatment effect waning (TEW) is applied in the base-case so that only the selected parametric functions, cure assumption and background mortality rates determine time in disease-free state. The key justifications for allowing the treatment effect of adjuvant Pembrolizumab to be sustained over time are as follows:

- TEW has not typically been applied in NICE appraisals of pembrolizumab in early stage settings. No treatment waning assumption was applied to neoadjuvant or adjuvant pembrolizumab in TA766, TA837 or TA851. It was explored in TA830 where cure assumptions were not applied and was examined in sensitivity analysis in TA823, but no details on the committee's preferences are available in FAD.
- TEW is already effectively being applied after the cure point as a cure point equalises hazards. TEW is justified when the hazards of progression events are thought to no longer differ between arms and the convention across immunotherapy appraisals is to apply this many years after the observed data period. For pembrolizumab, the latest NICE committee assumptions in the metastatic setting are to impose this 3-5 years after treatment cessation (TA939).[90] As summarised in Table 16, KEYNOTE-091 includes follow up data up to 84.2 months (for the prior adjuvant chemotherapy population) i.e. 6 years post-cessation of pembrolizumab, and shortly beyond this the hazards will begin to equalise due to cure assumptions. It is worth noting that there is no evidence in support of either the existence or the timing of treatment effect waning in immunotherapy. Given all patients in this indication have been treated with curative intent, a cure assumption is a much more logical, evidence-based way to equalise the long-term hazards between the arms.
- The mechanism of action of Pembrolizumab supports a sustained treatment effect. Studies in the metastatic setting have identified high objective response rates (ORR)

in patients receiving chemotherapy having been exposed to immune checkpoint inhibitors compared with patients who only received prior chemotherapy. There are different hypotheses supporting this phenomenon, including increased pool of activated T cells or increased tumour sensitivity to subsequent therapies induced by exposure to anti-PD1. Detailed explanation is presented in section B.3.3.2. [91]

- Observed KEYNOTE-091 trial data supports a sustained treatment effect. The 5 years of KEYNOTE-091 follow-up data show a sustained separation in DFS and OS curves, so a post-discontinuation treatment effect is plausible. There is no clear indication of a waning of treatment effect in either outcome.

- Long-term data from historic Pembrolizumab indications support a sustained treatment effect. Longer term data from other KEYNOTE clinical trials have shown a continued treatment effect post-discontinuation of pembrolizumab treatment both in the early and late-stage disease. For example some indicative studies include:

    - In KEYNOTE-522, a trial of peri-adjuvant pembrolizumab + chemotherapy versus neoadjuvant chemotherapy for early-stage triple-negative breast cancer, the HR for event-free survival remained consistent at 0.63 across interim analyses (median follow up, months: IA2, 15.5; IA4, 39.1; IA6, 63.1), following treatment discontinuation after 14 months.[92]

    - In the KEYNOTE-716 trial among patients with completely resected high-risk stage IIB/IIC melanoma, adjuvant pembrolizumab demonstrated a sustained treatment effect on recurrence-free survival versus placebo over 3 years of follow up between the first and most recent interim analyses, after treatment discontinuation at 1 year (HR: IA1 14.4 months, 0.65; IA4 39.4 months, 0.62).[93]

    - KEYNOTE-006 represents the longest follow-up (median 7 years) from a phase 3 trial of anti-PD-1/L1 therapy for advanced melanoma available to date. [94] The long-term outcomes observed in KEYNOTE-006 with patients treated up to 2 years is generally consistent with those observed in the melanoma cohort of KEYNOTE-001, which did not include a 2-year stopping rule. [95, 96]

    - In KEYNOTE-024 (a trial of pembrolizumab monotherapy in PD-L1 ≥50% NSCLC), there was no narrowing of the PFS treatment benefit of pembrolizumab monotherapy versus chemotherapy through 5 years of follow-up (HR at 11.2 months was equal to the HR at 5 years, with a sustained separation of the

curves), despite a high degree of crossover to pembrolizumab among those who progressed on chemotherapy.[62, 97, 98]

Modelling transitions from local-regional recurrence

In KEYNOTE-091, follow-up imaging data was not routinely collected once patients had experienced local-regional recurrence as their first event. As a result, the subsequent transition probabilities from local-regional recurrence to distant metastases or directly to death were unavailable from the trial. This is a consequence of the trial design and is consistent with other adjuvant NSCLC NICE appraisals such as the atezolizumab (TA823)[99] and osimertinib (TA761).[89] Similar to the atezolizumab and osimertinib models, external data needed to be sourced for the LRR to DM and DM to death transitions. We undertook Real-world Data analysis from the SEER-and Medicare [100] database, hereafter referred to as 'SEER-Medicare' which links population-based data of cancer patients in the SEER program and their matched Medicare administrative claims data. This allows a longitudinal assessment of diagnoses (such as site, staging), treatments (i.e. cancer-directed surgery and radiation therapy for first course of treatment), and service use before and after the cancer diagnosis . [101]From this database, we applied inclusion criteria to ensure patients were aligned with the KEYNOTE-091 population i.e. patients with completely resected stage IB-IIIA NSCLC AJCC 7th Edition (with or without receipt of adjuvant chemotherapy) and as having a local-regional recurrence at least 30 days prior to any metastatic occurrence. Full details of the inclusion criteria and baseline characteristics of those who had a local-regional recurrence are detailed in Appendix O. In total, 1,761 patients met the criteria and of these, 392 were subsequently identified as having a local-regional recurrence at least 30 days prior to any metastatic occurrence and were included in the transition probability estimation for LR to DM and LR to death. Given that the analytical sample for estimating LR to DM and LR to death rates only included patients who experienced local-regional recurrence, this sample was not further restricted to patients who had received adjuvant chemotherapy due to small sample size.

Estimation of transition probabilities from local-regional recurrence

Of these 392 patients, exponential competing risks models were then fitted for the transitions from LR to DM and LR to death. We assumed the exponential distribution to estimate these transitions as this is commonly used, particularly where these transition probabilities are being estimated from intermediate health states in a Markov model, as the hazard rates do not depend on time since entry into the health state. When the cause-specific hazards of LR to DM and LR to death were modelled, patients were followed from the time of local-regional recurrence and were censored at the earliest of the competing event, loss of follow-up, and

end of follow up. The transition probability from LR to death was constrained to be at least as high as background mortality in each weekly cycle. The cause-specific hazards of LR to DM and LR to death as estimated based on SEER-Medicare data are summarised in Table 38.

Table 38. Transition probabilities (uncalibrated) starting from local-regional recurrence (SEER)[100]

LR to DM		LR to Death	
Weekly exponential rate (SE)	**SE**	**Weekly exponential rate (SE)**	**SE**
0.00526	(0.000347)	0.00160	(0.00019)

Abbreviations: DM, distant metastases; LR or LRR, local-regional recurrence; NSCLC, non-small cell lung cancer; SE, standard error. Note: The transition probability from LR to death within each cycle is set equal to the maximum of the estimated probability based on parametric modelling and background mortality (United Kingdom Life Tables, 2020).

Validation of SEER source with other external sources for LR transition rates

The LR transition rates from SEER were compared with a variety of sources, using the median months to progression and death from a range of partly comparable datasets used in other NICE TAs along with the baseline characteristics and treatments received in each source and these are summarised in Table 39. These medians were first converted to a monthly rate assuming exponential distribution and then adjusted to a weekly rate.

The atezolizumab submission (TA823) calculated probabilities of transition from LR state to DM and death were based on two small single centre studies from Japan and the USA, Nakamichi et al. (2017) [102]and Kruser et al. (2014).[103] Nakamichi et al. (2017) analysed 74 NSCLC patients with postoperative LR events who received chemoradiotherapy or radiotherapy, whilst the latter study included 37 NSCLC patients who received radiotherapy following local-regional recurrence. Moore et al. (2020) [104] is a more recent Canadian retrospective cohort study and followed 179 patients after local recurrence and treatment with curative intent (surgery or radiotherapy with or without chemotherapy). The osimertinib submission (TA761) used a real-world database (CancerLinQ) of patients with EGFRm-positive NSCLC in stage IB–IIIA following tumour resection (who had experienced local-regional recurrence). Durvalumab (TA798) was recommended by NICE for patients with locally advanced unresectable NSCLC (PD-L1 >=1%) whose disease has not progressed after platinum-based chemoradiation. TA798 presents mature PFS and OS KM data from the pivotal PACIFIC trial[105]. At the 2023 Clinical Advisory Board, the advisers confirmed that none of these datasets can be considered wholly reliable due to indirectness of the patients or outcomes captured.

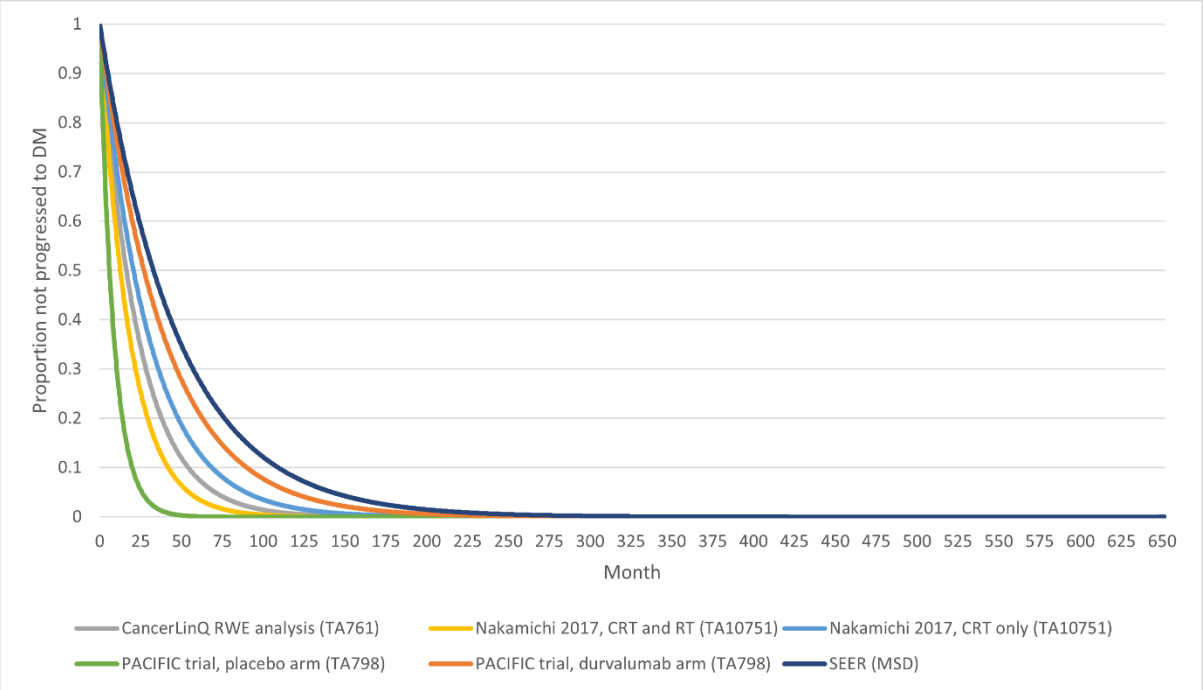
Table 39. SEER [100] versus other external sources for LR rates to DM and LR to death

Sources	Progression (LR to DM)		Overall survival (LR to Death)	
	Median progression (m)	Estimate weekly rate	Median OS (m)	Estimate weekly rate
Used in the base-case				
SEER (without calibration)	N/A	0.00526	N/A	0.00160
Other external sources				
CancerLinQ database analysis (TA761)	15	0.011	N/R	N/R
Nakamichi 2017, CRT and RT (TA823)	11.6	0.014	34.4	0.005
Nakamichi 2017, CRT only (TA823)	19	0.008	79.6	0.002
Kruser 2014 (TA823)	N/R	N/R	5.1	0.031
PACIFIC trial, durvalumab arm (TA798)	24.9	0.006	63.1	0.003
PACIFIC trial, placebo arm (TA798)	5.5	0.029	29.6	0.005
Moore 2020, curative	N/R	N/R	34.3	0.005
Moore 2020, palliative	N/R	N/R	9.8	0.016

Abbreviations: DM, distant metastases; LR or LRR, local-regional recurrence; N/R: not reported; SE, standard error; m, months. Notes: medians are converted to rates (assuming an exponential distribution) using the formula rate = Ln(2)/(median time). The median from the CancerLinQ analysis is taken from the KM (figure 26, company submission) in TA761. Month rates are converted to week rates by diving by (365.25/12/7).

As indicated in Table 39, though the estimated weekly LR to DM rate from SEER is the lowest of the external sources, the most similar are the durvalumab arm in the PACIFIC trial and the control arm of the study by Nakamichi used in the atezolizumab appraisal. The implied LR to DM exponential curves for the various sources are illustrated in Figure 12. The clinical experts from the 2023 Clinical Advisory Board confirmed the SEER source as having the patient characteristics that were most applicable to LR patients in our model (seen below in navy blue).

Figure 12. Other external sources for LR to DM movement (converted to weekly probabilities)



Modelling transitions from distant metastases

In each adjuvant treatment arm, the transition probability from distant metastases to death was assumed to depend on the distribution of first-line treatments for metastatic NSCLC received in that arm. The model also considered the cost of second-line therapies for metastatic NSCLC in each adjuvant treatment arm; however, survival within the distant metastases state was assumed to depend on the choice of first-line therapy only. This limitation is only minor because no important second-line options have become available since the approval of regimens for first line metastatic NSCLC. The OS curves from these trials are therefore still considered generalisable.

B.3.3.2. Subsequent treatment market shares in distant metastases health state

First line

First and second-line treatment proportions for patients who progress to DM were estimated using clinical expert opinion elicited in the 2022 Clinical Advisory Board[45], proportions of different mutation/expression types in the population, and some simplifying assumptions.

It is important to note that patients in this decision problem are all theoretically eligible for treatment with adjuvant I/O. We therefore assumed that no patients were contraindicated to I/O treatments downstream e.g. by having autoimmune conditions.

In particular, the 2022 Clinical Advisory Board supported the view expressed in the atezolizumab (TA823) appraisal Committee meeting that the NHS would allow rechallenge with an (anti-PD-1/PD-L1) I/O if relapse had taken place 6 months after the end of treatment with adjuvant I/O (in this case pembrolizumab). This criterion is also now included in the relevant Blueteq forms for metastatic I/O treatments.[106] Treatment proportions are for 1L DM and 2L DM and for I/O eligible (post 18-month progressors in the pembrolizumab arm and all patients in the placebo arm) are summarised in Table 40.

- I/O-eligible: patients who have never received adjuvant pembrolizumab (i.e. active monitoring arm) or who transition to DM after having achieved at least 18 months since the start of the model.

- I/O-ineligible: patients who transition to DM within 18 months in the pembrolizumab arm.

Table 40. Subsequent treatment market shares by I/O eligibility status and adjuvant treatment arm

	Pembrolizumab[45]		**Active monitoring**
First line:	**I/O-eligible (1L)**	**I/O-ineligible (1L)**	**I/O-eligible (1L)**
Osimertinib	15%	15%	15%
Pembrolizumab + carboplatin + paclitaxel	32.6%	0%	32.6%
Pembrolizumab + pemetrexed + platinum	52.4%	0%	52.4%
Carboplatin + paclitaxel	0%	32.6%	0%
Pemetrexed + platinum (PDC)	0%	52.4%	0%
Second line:	**IO-eligible (2L)**	**IO-ineligible (2L)**	**IO-eligible (2L)**
Docetaxel	30%	30%	30%
Pemetrexed + platinum	30%	30%	30%

No active treatment (BSC)	40%	40%	40%

Abbreviations: I/O, immunotherapies; 1L, first line; 2L second line; PDC, platinum doublet chemotherapy

In both I/O-eligible categories in the pembrolizumab and placebo arms in first-line DM, 15% are assumed to receive a targeted therapy for EGFR, KRAS G12C, ALK, ROS-1 positive NSCLC. All these mutation types have targeted therapy recommendations in first line treatment. For computational simplicity, efficacy and costings for this 15% are assumed to be associated with osimertinib, which is the treatment of choice for the most common marker, EGFR. It is important to note that whatever bias might be introduced by this simple approach is moderated by the small proportion that receive targeted therapy and that the proportions are the same between the arms. The remaining I/O-eligible patients who do not receive a target therapy (85%) are split as follows in 1L:

- 32.6% are squamous patients who will receive pembrolizumab with chemotherapy (pembrolizumab + carboplatin + paclitaxel). This was informed by the proportion of patients who are squamous from the PD-L1 TPS < 50% baseline characteristics from KEYNOTE-091 trial as summarised in Table 10.
- 52.4% are non-squamous patients who receive pembrolizumab with PDC (pemetrexed + platinum chemotherapy). The market share was informed by the subtracting the 15% targeted therapy patients from the overall proportion with non-squamous disease.

Pembrolizumab I/O-ineligible

For the I/O-ineligible patients in the pembrolizumab arm, we assumed 15% of patients receive osimertinib (same as the I/O-eligible market shares). We also assumed patients receive chemotherapy (i.e. the placebo arms) of the pembrolizumab combinations i.e. carboplatin + paclitaxel and pemetrexed + platinum as these patients cannot receive I/O in 1L. For simplicity, these chemotherapies were assigned the same market shares as the pembrolizumab combinations.

Second line

In second line, given the fitness of patients by this stage, a fixed proportion of 40% are assumed to receive BSC irrespective of arm or I/O eligibility status. Advice at the 2022 Clinical Advisory Board[45] supported a 30-40% range. Second-line patients are assumed to receive no targeted treatments or I/Os as all eligible patients will have received them at first line and therefore the remaining 60% were divided evenly between docetaxel and platinum doublet chemotherapy.

Estimation of survival by first-line treatment for metastatic NSCLC

For each metastatic first-line NSCLC treatment option, exponential models of OS and progression-free survival (PFS) were estimated using the following approach:

- Three first-line treatment options were designated as reference treatments (Table 41): pembrolizumab + pemetrexed + platinum (for non-squamous NSCLC); pembrolizumab + carboplatin + paclitaxel (for squamous NSCLC) and osimertinib (for EGFR+ NSCLC). For each of these treatments, weekly exponential rates of OS and PFS failure were computed as a function of the median OS and PFS reported in the pivotal clinical trials of each treatment.

- For the remaining metastatic treatment regimens in first line, Pemetrexed + platinum (for non-squamous patients having chemotherapy) and Carboplatin + paclitaxel (for squamous patients having chemotherapy), HRs for OS and PFS vs. the corresponding pembrolizumab reference treatment were obtained from within trial hazard ratios for the PD-L1 < 50% population [107].

Table 41. Exponential models of OS and PFS with reference treatments in the 1L metastatic NSCLC setting

Metastatic regimen	Indicated population strata	Exponential rate of death	Exponential rate of death or progression	Sources
		Weekly rate (SE)	Weekly rate (SE)	
Pembrolizumab + pemetrexed + platinum	Non-squamous PD-L1 < 50% NSCLC	0.0081 (0.0007)	0.0197 (0.0015)	KEYNOTE-189 data on file (data cut-off date: 08 Mar 2022)
Pembrolizumab + carboplatin + paclitaxel	Squamous PD-L1 < 50% NSCLC	0.0097 (0.0008)	0.0245 (0.0018)	KEYNOTE-407 data on file (data cut-off date: 23 Feb 2022)
Osimertinib	EGFR+ NSCLC (assumed efficacy for proportion on targeted therapy)	0.0041 (0.0002)	0.0084 (0.0008)	Ramalingam et al. (2020) [108] & Soria et al. (2018) [109]data on file [FLAURA]

Abbreviations: EGFR: epidermal growth factor receptor; NSCLC; non-small cell lung cancer; PD-L1: programmed death-ligand 1; SE: standard error

Table 42. HRs of OS and PFS with reference treatments in the 1L metastatic NSCLC setting

Metastatic regimen	Indicated population strata	HR of death	HR of death or progression	Sources
		SE of ln (HR)	SE of ln (HR)	
Pemetrexed + platinum	Non-squamous PD-L1 < 50% NSCLC	1.69 (0.12)	1.59 (0.12)	KEYNOTE-189 data on file (data cut-off date: 08 Mar 2022)
Carboplatin + paclitaxel	Squamous PD-L1 < 50% NSCLC	1.41 (0.11)	1.54 (0.11)	KEYNOTE-407 data on file (data cut-off date: 23 Feb 2022)

Abbreviations: NSCLC; non-small cell lung cancer; PD-L1: programmed death-ligand 1; SE: standard error

In each model arm, the HR of DM to death was assumed to depend on a combination of both i) subsequent market shares of first-line treatments (as indicated in Table 40) and ii) the expected survival associated with each metastatic NSCLC treatment regimen (as indicated in Table 41). Specifically, the weekly hazard of OS (starting from distant metastases) was calculated in each adjuvant treatment arm as a weighted average of the weekly OS hazard associated with different first-line treatments for metastatic NSCLC, based on the market shares of first-line advanced treatments in that arm. The weighted exponential hazard rate for DM to death based on market share is summarised in Table 43.

Table 43. DM to death weighted exponential HR based on market share

Patient Group	Distant metastases → death: Weighted exponential hazard rate based on market share
Pembrolizumab (I/O eligible)	0.0074
Pembrolizumab (I/O ineligible)	0.0101
Placebo	0.0074

The use of weighted exponential rates is a necessary simplification due to the Markov model structure. It should be noted that the trials underpinning the DM health state transitions did not typically enrol resected patients, but the direction and extent of any bias on treatment effects introduced by this generalisability concern is unknown.

Expected PFS in the DM state was also estimated using median PFS data from the trials, with the weighted rate for each model arm was based on the distributions of first-line

treatments received. This was needed to calculated overall DM health state utility and resource use. The ratio of mean PFS to mean (pre-adjustment) OS calculated via the area under the exponential survival curves was calculated for each treatment and therefore weighted expected PFS and OS could be calculated for each model arm. The ratio of PFS to OS was used to weight pre-progression and post-progression DM utility values to calculate overall utility values along with the weekly disease management costs, as described in B.3.4 where separate utility and resource use estimates are available for patients pre progression (termed “DM1”) and post-progression (termed “DM2”).

Adjustment to observed SEER-Medicare data

We queried the SEER-Medicare database to validate the weekly OS rates among resected patients who had progressed to DM (see Appendix O for methodology). The database showed that these patients appeared to have longer median OS than those in the 1L mNSCLC clinical trials, despite no better treatment being available in the SEER-Medicare setting. This may be because patients who have been resected are regularly monitored and metastatic disease is caught much earlier than among the *de novo* metastatic patients who were enrolled into clinical trials. It is common for lung cancer with a limited extent of disease to be asymptomatic, which is why so many patients are diagnosed at stage IV and/or in A&E. [19, 110, 111]To account for this apparent underlying difference in prognosis, we investigated applying a universal adjustment factor to all patients in the metastatic health state. The adjustment factor was calculated by dividing the rate observed in SEER-Medicare by the rate predicted for DM patients in the control arm of the model based on market share data. In the base-case, we applied this adjustment factor to all DM->Death transitions in both arms to reflect the relatively better prognosis of this heavily monitored population.

Calibration of downstream transitions to observed OS

We initially set the model up to assume no ongoing benefit from exposure to pembrolizumab in the adjuvant setting i.e. the transition probabilities in the downstream health states were largely the same and therefore the mechanism by which pembrolizumab was modelled to affect OS was purely through its effect on DFS.

In order to validate this assumption, we examined the fit of the modelled OS curves vs. the observed OS curves from KEYNOTE-091, noting that many years of OS data are now available from KEYNOTE-091. We noticed that the observed OS in the active monitoring arm was predicted well by the economic model regardless of DFS curve selection choices, which suggests that the model reasonably accurately characterises the natural history of resected NSCLC in the current pathway. The pembrolizumab arm, however, was always significantly underpredicted. Since DFS in both arms is modelled very accurately in the

economic model, this suggests that patients in the pembrolizumab arm of KEYNOTE-091 who had an LR or DM event had better post-event outcomes than those who had an LR or DM event in the placebo arm, at least within the time horizon of the trial.

At first, we examined whether this was due to the model imposing no retreatment with immunotherapy within the first 18 months and whether retreatment was common in the trial. We found that firstly, allowing retreatment in the model improved the fit slightly but did not solve the calibration issue (Figure 13) and secondly, that retreatment with I/O was relatively uncommon in the pembrolizumab arm of the trial ([redacted]% as a proportion of total recurrences vs [redacted]% in the control arm; many of these could have occurred after the 18 month cutoff anyway), which suggests the observed data are not explained by this.

Figure 13. retreatment with I/O allowed from t=0 in the pembrolizumab arm still results in underfitting of pembrolizumab OS

[redacted]

We discussed this problem with the EAG at the Decision Problem Meeting, who advised us to look for evidence explaining this effect and to ensure we presented evidence that this effect might be observed in UK clinical practice and was not a trial specific effect e.g. caused by treatments that are not available in the NHS or some other generalisability issue.

We also discussed this with the 2023 Clinical Advisory Board[46] and on a call with an investigator on KEYNOTE-091. The advice we received was that it was considered clinically plausible that there would be some residual benefit from exposure to pembrolizumab that was not fully captured in the DFS outcome alone. Multiple explanations were suggested by clinicians:

1. The mechanism of action of immunotherapy is such that it fundamentally modifies the disease course. This could affect prognosis by:
    a. slowing progression of the disease in general or
    b. meaning that patients recurred at stages where radical treatment was either more possible or more effective.
2. Immunotherapy is known to improve patients' sensitivity to chemotherapy in NSCLC. This means that treatments patients received downstream, chemo-radiotherapy for example, could be more effective.

We conducted some analysis on the KEYNOTE-091 clinical trial database to try to understand whether patients in the LR state were occurring at earlier stages or whether they were more likely to have received radical interventions in the pembrolizumab arm and did

not find any conclusive evidence (Table 44). Stage at recurrence was not available and many patients had no subsequent treatment recorded.

Table 44. Summary of First Subsequent Oncologic Therapies - Participants With Loco-regional Recurrence for Disease-free Status (Primary Censoring Rule) Based on Investigator Assessment – Overall Population (All-Participants-as-Treated Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Participants who had any subsequent oncologic therapies for NSCLC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First Subsequent Chemoradiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First Subsequent Drug Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First Subsequent Radiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First Subsequent Surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Subsequent chemoradiation includes participants who received drug therapy and radiotherapy concurrently or sequentially as first subsequent regimen.

Subsequent systemic therapy includes participants who received drug therapy as first subsequent therapy after and do not fulfil the criteria for subsequent chemoradiation.

Subsequent radiotherapy includes participants who received radiotherapy as first subsequent therapy.

Subsequent surgery includes participants who received surgery as first subsequent therapy.

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report.[66]

We then queried the patients who had a DM event to understand whether they had any prognostic characteristics that appeared more favourable in the pembrolizumab arm. Among patients with DM events, we found a lower proportion of patients with brain metastases, which is a stratification factor in trials in the advanced setting, in the pembrolizumab arm but the magnitude of difference in proportion was not large.

Table 45. Summary of Participant's Distant Metastases – PD-L1 TPS < 50% Subpopulation Experiencing Distant Metastases (ITT Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]	[redacted]	[redacted]		[redacted]	
Brain Lesions						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lesions						
Single	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Participants who experienced a DFS event classified as distant metastasis.

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report.[66]

Overall, granular data on stage of disease on recurrence was not available and a large proportion of patients appeared to have subsequent treatment not recorded. Taken together, there was not sufficient evidence to validate or invalidate the hypothesis that pembrolizumab patients have a post-DFS benefit outside of the fact that this phenomenon has been observed in the trial.

At the Decision Problem Meeting, the EAG asked us to investigate whether there could have been trial-specific factors such as availability and use of subsequent therapies that would mean this phenomenon would not be observed in UK clinical practice. We understand this to mean therapies that would improve survival in the pembrolizumab arm that wouldn't be available in the UK. We examined the subsequent treatment data from the trial and note that treatment rates with high-cost drugs appear to be very low in the pembrolizumab arm. More specifically, of the patients in the PD-L1 TPS<50% subpopulation that progressed to DM in the pembrolizumab arm (n=[redacted]), only [redacted] ([redacted]%) patients received a 1L subsequent treatment that does not reflect UK clinical practice and is expected to have high costs i.e., atezolizumab plus carboplatin plus paclitaxel, bevacizumab plus carboplatin plus paclitaxel, pemetrexed plus ipilimumab plus nivolumab and cabozantinib (Appendix M, Table 67). We also examined the subsequent treatment data in the trial patients (overall population) that progressed to LR (n=[redacted]). Although we cannot determine how many of these patients further progressed to DM (DF→LR→DM), subsequent treatments after 1L are likely to have been administered to patients that further progressed to DM. Consistent with what was described previously, only a low proportion of patients in the pembrolizumab arm (n=[redacted]%]) received a high-cost therapy in 2L not reflecting UK practice (i.e. bevacizumab plus carboplatin plus pemetrexed, bevacizumab plus pemetrexed, docetaxel plus ramucirumab and reprotectinib) (Appendix M, Table 66). It is worth noting that none of these non-NICE approved therapies are expected to be more effective than standard care in the UK, for example pembrolizumab with/without chemotherapy, and therefore they are unlikely to be associated with the post-DFS survival advantage observed in KN091. The subsequent treatments in the placebo group are similarly representative of UK clinical practice.

Our interpretation of these data is that there is no evidence that the apparent post-DFS survival advantage observed in KN091 is caused by trial-specific factors such as the availability of treatments that are not available in the NHS. KEYNOTE-091 is also a large enough RCT that we can be confident that the apparent differences are not caused by

imbalances in baseline characteristics between the trial arms. It may therefore be reasonable to assume this phenomenon would be observed in the NHS.

Here we present scientific data in support of the concept of a post-DFS benefit for pembrolizumab.

We identified relevant papers by first examining citations in the article by Park et al[112], which was highlighted as a reference during discussions with a clinician. We then performed a literature search of the PubMed database in February 2024 for publications within the past 10 years using the search terms [((((chemotherapy after exposure to immune checkpoint inhibitors) OR (salvage chemotherapy)) OR (chemotherapy after anti-pd1)) OR (chemotherapy after anti-pd-l1)) AND (advanced nsclc) NOT (salvage surgery) NOT (Radiotherapy) NOT (Radiation) NOT (rechallenge) NOT (SCLC) NOT (Mesothelioma)] with 139 results. Manual exclusion of [review articles / combination with other targeted therapy or immunotherapy besides anti-PD-(L)1 / non-NSCLC / did not have Immune Checkpoint Inhibitors (ICI) in the 1L setting / rechallenge or re-administration of ICI / non-English language articles] resulted in 4 studies, 2 being additional to those cited by Park et al.

The studies identified high ORR in patients receiving chemotherapy having been exposed to immune checkpoint inhibitors compared with patients who only received prior chemotherapy. Historically, ORR on repeat chemotherapy has generally been low: Borghaei et al. noted an ORR of 12% in docetaxel control arm in patients who had progressed during or after a first-line platinum-based chemotherapy regimen.[113] Rittmeyer et al. determined an ORR of 13% in docetaxel control arm in previously treated patients with NSCLC.[114] KEYNOTE-010, a study of pembrolizumab vs. docetaxel following progression on platinum doublet chemotherapy noted an ORR of 9% in the docetaxel arm.[115] Similarly, a 9% ORR was reported in patients receiving docetaxel who had disease recurrence after one prior platinum-containing regimen.[116]

Schvartsman et al. demonstrated an ORR to single-agent chemotherapy after exposure to anti-PD1 of 39% (11/28 patients).[117] Park et al noted an ORR of 66.7% (16/24) in patients receiving salvage platinum-doublet chemotherapy administered after immunotherapy. Similarly, Grigg et al. confirmed an ORR of 25% in patients with mNSCLC who received at least one dose of anti PD(L)-1 and subsequent chemotherapy.[118] Leger PD et al. identified an odds ratio of 0.30 for achieving a partial response in patients receiving salvage chemotherapy following PD-(L)1 inhibitors versus patients receiving salvage chemotherapy who had not been exposed to PD-(L)1 inhibitors.[119] Diker et al. described an ORR of 20.0% in a retrospective study of 21 patients who had received at least one dose of salvage chemotherapy after immunotherapy.[120] Whilst this is lower than the other studies, it is worth

noting that the majority (62.9%) of patients were ECOG PS 2. Finally, Heraudet et al. identified an ORR of 18.3%, 24%, 33% and 18% in patients with previous immune checkpoint inhibitor exposure who subsequently received paclitaxel-bevacizumab, paclitaxel, pemetrexed and gemcitabine, respectively.[121]

There are several scientific proposals which may explain how prior exposure to a PD-1 axis inhibitor may affect response to subsequent lines of therapy. One hypothesis is an increased pool of activated T cells induced by exposure to an anti-PD1 may lead to improved response rates (Schvartsman et al., 2017).[117] Another hypothesis is that PD-1 axis inhibitors activate the immune system and change the tumour microenvironment resulting in increased tumour sensitivity to subsequent therapies (Saleh et al., 2018). [122] The evidence discussed has been generated in the metastatic setting as there is currently limited data on the residual treatment effect of pembrolizumab-exposed patients in the early-stage setting. However, we anticipate these data would translate to earlier stages of treatment. Since many patients will receive chemotherapy, chemo-radiotherapy or immunochemotherapy in later lines of treatment, it is plausible that their prognosis might be better in the pembrolizumab arm.

We decided to implement a calibration technique to ensure that the economic model captured the observed data for the pembrolizumab arm accurately since the study is deemed generalisable in the UK setting and clinicians expected the OS trajectory to match that seen in KN-091. We felt sure that if the economic model was overpredicting OS in the pembrolizumab arm alone the NICE committee would be interested in an analysis where the modelled outcomes were calibrated downward to match the observed outcomes and so the same should be true for the reverse situation.

The economic model includes the ability to calibrate the downstream transitions, either LR→Death alone, both LR→DM and LR→Death or LR→DM, LR→Death and DM→Death simultaneously. The model arms are calibrated separately and, except in the scenario where the LR->Death transition was calibrated alone, the ratio between the LR→DM and LR→Death transition was held constant in every iteration of the calibration algorithm to preserve consistency in that relationship. In each iteration, the algorithm applied a multiplicative factor in increments of 0.01 between 0.01 and 3 to the one, two or three transition probabilities being tested in each arm and reported a Mean Squared Error (MSE) statistic, which was weighted by patients at risk at each weekly time point along the OS KM curve. We imposed a cap of 7 years on this calibration to match maximal follow-up in the trial and to be conservative given the general uncertainty about this approach. The rescaling factor is tapered linearly from 5 years to 7 to match the method used in the cure assumption.

For each of the three possible calibrations, the one implemented in the model is based on the rescaling factor with the minimum weighted MSE. We assessed the visual fit to the OS curve along with the clinical plausibility of the rescaled transition probabilities. We noted that, when only calibrating transitions in the LR state, the transition probabilities in the pembrolizumab arm appears extremely low versus the original real-world data sources. When the DM→Death transition was included, the difference between the calibrated TPs and original TPs was not that large. **We concluded that temporarily calibrating all three transitions at once was the most appropriate approach and produced good visual fit to the OS curves.**

The calibration can be run either with or without the DM→Death probabilities in the placebo arm having been rescaled to adjust for the improved survival outcomes among patients in the target population who develop distant metastases using the data observed in SEER-Medicare (Section B.3.3.2). First, we ran the calibration including this adjustment and then without it and examined the resulting rescaled transition probabilities.

Inclusive of the SEER-Medicare adjustment, the result was a calibration factor of 0.82 applied to all downstream TPs in the pembrolizumab arm and a calibration factor of 1.21 applied to downstream TPs in the placebo arm.

Included in the below figures is an OS curve based on Real-world Data from the SEER database in stage IB-IIIA patients following surgery. This cohort were on average 9.4 years older than those in KEYNOTE-091, which is likely the source of the slightly overpredicted base-case OS in the placebo arm.

Figure 14. Completely uncalibrated modelled OS vs. observed OS

[redacted]

Figure 15. Real-world adjustment factor from SEER applied to both arms vs. observed OS

[redacted]

Figure 16. Real-world adjustment factor and calibration applied to both arms vs. observed OS

[redacted]

Table 46.SEER-Medicare adjustment factor for HR of DM to death

Parameter	Value	Source
Weekly hazard rate of DM → death observed in real-world cohort study, [a]	0.0052	Analysis of SEER Medicare database

Unadjusted weekly hazard rate of DM → death estimated for the placebo arm in the receiving adjuvant chemotherapy population, based on first-line metastatic NSCLC treatment efficacy and market shares, [b]	0.0074	Calculated based on first-line metastatic NSCLC treatment efficacy and market shares for the placebo arm in the receiving adjuvant chemotherapy target population
Adjustment factor (hazard ratio of [a] : [b])	0.7017	Calculation based on values above

Table 47 shows the weighted weekly rates before and after the two-step process of adjustment and temporary calibration.

Table 47.Weighted weekly rates before and after adjustment and temporary calibration

Patient Group	Calibrated LR->DM	Calibrated LR->D	Distant metastases → death: *Weighted exponential hazard rate based on market shares*	Real-world adjustment factor (based on SEER)	Distant metastases → death: *After applying real-world adjustment factor*	Temporary calibration factors (base-case scenario - both arms)	Distant metastases → death: *After applying real-world adjustment factor and calibration factor*
Pembrolizumab (I/O eligible)	0.0043	0.0013	0.0074	0.70172	0.0052	0.82000	0.0043
Pembrolizumab (I/O ineligible)	0.0043	0.0013	0.0101	0.70172	0.0071	0.82000	0.0058
Placebo	0.0064	0.0019	0.0074	0.70172	0.0052	1.21000	0.0063

If not calibrating the downstream transitions to SEER, the algorithm can be re-run and produces the transitions in Table 48.

Table 48. Company base-case transition probabilities

Patient Group	Calibrated LR->DM	Calibrated LR->D	Distant metastases → death: *Exponential hazard rate based on expected OS*	Calibration factor *(if applied)*	Distant metastases → death: *After applying calibration factor only*
Pembrolizumab (I/O eligible)	0.0033	0.0010	0.0074	0.63000	0.00467
Pembrolizumab (I/O ineligible)	0.0033	0.0010	0.0101	0.63000	0.00639
Placebo	0.00478	0.0015	0.0074	0.63000	0.00674

Figure 17 shows that the long-term OS, fit to observed OS and fit to real-world data remains the same.

Figure 17. OS when calibrating using only the algorithm and not SEER (company base-case)

B.3.3.3. Time on treatment

The proportion of patients remaining on adjuvant pembrolizumab at each scheduled infusion was based on the observed Kaplan-Meier curve for time to treatment discontinuation in the KEYNOTE-091 trial. In the trial, patients randomised to adjuvant pembrolizumab received treatment for a maximum of 18 doses (approximately 1 year). Based on this maximum duration, there were no patients remaining on treatment as of the data cut-off date; thus, the observed Kaplan-Meier curve for time on treatment (ToT) was fully mature and could be used directly, without the need for extrapolation.

As illustrated by Figure 18 a small percentage of patients in the pembrolizumab arm of KEYNOTE-091 (data cut-off -2023) remained on adjuvant therapy beyond 1 year, even though no patients in the trial received more than 18 doses. This result occurs because the protocol allowed patients to complete all 18 doses past the 1-year point if there had been earlier delays in treatment. Within the model, the costs of adjuvant pembrolizumab treatment were applied at fixed intervals of every 3 weeks starting with the first infusion at cycle 0, and so the cost of the 18th dose was applied at t = 51 weeks for the percentage of patients still on adjuvant treatment at 51 weeks. If, for example, a patient's 18th dosage was delayed to 54 weeks, the cost of their 18th dosage is still applied at 51 weeks within the model. The model therefore does not use the portion of the Kaplan-Meier curve beyond the scheduled 1-year treatment period (represented by the dashed line in Figure 18), but all adjuvant Pembrolizumab drug use is reflected in the costing. The model includes the ability to either assume 100% Relative dose intensity and cap the KM curve at 52 weeks or to use the whole of the KM curve but adjust the proportion receiving treatment by a Relative Dose Intensity of 97.8%, which was observed in the trial. Both methods lead to very similar total pembrolizumab costs.

Figure 18. Kaplan-Meier curve for time on treatment (ToT) with adjuvant pembrolizumab

B.3.3.4. Adverse events

The model base-case includes all-cause grade 3+ AEs that occurred with a frequency of ≥1% in any of the KEYNOTE-091 arms (all-participants-as-treated population) as

summarised in Table 49. Mean duration per AE episode and mean number of episodes per patient with each included AE were collected from KEYNOTE-091 and were used within the model to estimate the duration of the disutility impact from each AE regardless of adjuvant treatment arm. This is conservative given that the impact of AEs would already be captured in the KEYNOTE-091 derived mean utilities applied for the health states as described in Section B.3.4.1. The percent of AEs resulting in hospitalisations were also collected from KEYNOTE-091 and were used to calculate the cost per AE episode in B.3.5.6. Utility decrements and costs are applied in the 1st cycle (in-line with standard practice).

Table 49. Adverse event incidence and durations (all cause grade 3+)

AE type	AE risk (%), by adjuvant treatment arm		Mean number of episodes per patient with AE	Mean duration of AE per episode (weeks)	% of AE episodes resulting in hospitalisation
	Pembrolizumab	Placebo			
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse events

B.3.4. Measurement and valuation of health effects

As described in B.3.1 an SLR was conducted (with the original SLR performed in 2021 and subsequently updated in 2022 and 2023) to identify published studies for evaluating cost-effectiveness, costs and resource use and health-related quality of life for treatments in NSCLC relevant to the decision problem. As the SLR search strategy combined the cost-effectiveness, HRQoL and costs and healthcare resource use searches, full details on the methodology of the SLR, including search terms are summarised in Appendix G. Full details on the findings of the HRQoL SLR including PRISMA diagram and outcomes are detailed in Appendix H. None of the studies reported HRQoL estimates consistently for adjuvant therapy except for '1L DM' health state from the osimertinib SMC appraisal which included a utility weight of 0.794 from the FLAURA trial and this was subsequently applied in the osimertinib NICE submission. As such, the primary source of HRQoL values used in the model was the pivotal KEYNOTE-091 using the Jan 2023 data cut off, which was collected

using the EQ-5D-3L instrument [123] in addition to KEYNOTE-189/407 trials, which are further described in Section B.3.4.1

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

KEYNOTE-091

Base-case utility values for the disease-free (without toxicity), local-regional recurrence, and distant metastases prior to any subsequent progression (pre-progression distant metastases) were derived using descriptive analyses of patient-level EQ-5D-3L data[123] KEYNOTE-091 with the UK algorithm applied. The base-case utility values for post-progression distant metastases were derived using EQ-5D-3L results (with UK based scoring) from the KEYNOTE-189/407 trials in the metastatic NSCLC setting.

Within KEYNOTE-091, at each visit where health state was assessed, the corresponding EQ-5D-3L score was used to measure utility. Instances where patient-visits with missing EQ-5D-3L responses were excluded. Utility values were calculated for the following states in KEYNOTE-091 based on the average across all patient-visits with an EQ-5D-3L measurement within that state:

- Disease-free (without AEs) - (N=5,273 patient-visits, includes patient-visits in the disease-free state while patients had no AEs or grade 1-2 AEs);
- Local-regional recurrence (N=463 patient-visits);
- Distant metastases (N=595 patient-visits)

In previous NICE appraisals, it has been considered appropriate to capture utility values for the disease-free state excluding visits where the patient was suffering from grade 1-2 AEs for several reasons. Firstly, the DF health state in adjuvant models has a very long time horizon compared to the time at which most EQ-5D data were collected. In this case, the model predicts more than 8 undiscounted mean life years in the DF state for the pembrolizumab arm whereas surgery related AEs should be time-limited and treatment is a maximum of one year, meaning that treatment-related AEs should only last this long. In KEYNOTE-091, 70% of EQ-5D forms filled in were collected in year 1. The utility value for those without grade 1-2 AEs may be more representative of the whole time horizon of the DF health state in the model, particularly because most of the disease free life years accrue to patients who have been cured and are not on any treatment. Grade 1-2 AEs are seldom included in TA submissions to NICE and the disutility and costs for grade 3+ AEs are captured separately in the model. This approach is consistent with NICE TA766[81] and TA837[79].

The utilities for each of the health states within the KEYNOTE-091 model are summarised in Table 50.

Table 50. Base-case and alternative health state utility values

Health state	Utilities		Sources
	Value	SE[1]	
Base-case			
Disease-free (without toxicity)	0.852	(0.010)	KEYNOTE-091 (mean excl AEs grades 1-2)
Local-regional recurrence	0.776	(0.026)	KEYNOTE-091 (mean)
Distant metastases (pre-progression)	0.743	(0.023)	KEYNOTE-091 (mean)
Distant metastases (post-progression)	0.668	(0.020)	KEYNOTE-189 & KEYNOTE-407 (pooled)[124, 125]
Health state	**Utilities**		**Sources**
	Value	**SE[1]**	
Alternative utilities available in the model			
Disease-free (with/without toxicity)	0.806	(0.007)	KEYNOTE-091 descriptive approach

Abbreviations: AE: adverse event; N/R: Not reported; SE, standard error. Note: [1] The SE of each health state utility input (as shown above) was calculated as 2 × the original trial-based SE of that utility input

The utility value for the distant metastases state from KEYNOTE-091 was used as an approximation of utility in the pre-progression distant metastases sub-state, as the available follow-up in KEYNOTE-091 was expected to be too limited to capture average utility over the entire post-progression disease course until death The base-case utility for post-progression distant metastases was instead derived from the KEYNOTE-189/407 trials, using a pooled average utility value across patient-visits within the post-progression distant metastases state. In each adjuvant treatment arm, utility in the distant metastases state was calculated as a weighted average of utility values in the pre- and post-progression distant metastases sub-states, based on the expected proportion of time spent pre- vs. post-progression within the distant metastases state (given the mix of first-line metastatic treatments received and the efficacy of those treatments). The method used to obtain the proportion of DM OS time spent progression-free is discussed in B.3.3.2.

B.3.4.2. Mapping

As per NICE's position statement for reference case analyses, the EQ-5D-3L value set is preferred for the reference case analysis. As stated in B.3.4.1 the EQ-5D-3L value set was used to collect HRQoL in KEYNOTE-091, therefore no mapping was performed.

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

The SLR methodology described in Appendix G with HRQoL results presented in Appendix H was conducted to identify studies reporting utility values for patients receiving adjuvant treatment for NSCLC. Only one study was found Leiter et al. (2022) which only reported disutilities for patients with local-regional NSCLC and smoking-related comorbidities therefore this did not contain any useful data to inform the economic model. For this reason, the economic evaluations and HTA reports included in the SLR were searched for relevant utility weights. Full details of the HRQoL estimates reported are provided in Appendix H but in summary the SLR identified 7 studies, 4 were UK-based HTA submissions (2 were NICE submissions; atezolizumab TA823 and osimertinib TA761 and 2 SMC submissions; osimertinib SMC2383 and atezolizumab SMC2492), 1 publication by the NICE Guideline Updates Team (2019) and the 1 from literature (Yip et al. 2023). [59, 74, 77, 89, 99, 126-129].

Utilities in the osimertinib models (NICE TA761[89], SMC2383[127]) were obtained by mapping SF-36 values from ADAURA to EQ-5D-3L; whilst these were also redacted, the company submission does state that the disease-free utility value is higher than the age-matched general population utility of 0.810, and that the same utility values was applied to both the disease-free and local-regional recurrence (LRR) states in the absence of reliable HRQoL data for the LR state from the clinical trial. Utility values for the pre- and post-progression DM states were sourced from the FLAURA trial (mapped from EORTC-QLQ-C30) and a study by Labbé et al, 2017[74], respectively. Mapping from a non-preference-based measure introduces additional uncertainty, and utility estimates in Labbé et al, 2017 were valued using a Canadian value set which is not aligned with the NICE reference case.

For the adjuvant atezolizumab models, HRQoL data were not available from the IMpower010 trial and therefore values from the literature were used. However, none of these sources aligned with the NICE reference case e.g. Jang et al. 2010 and Van den Hout et al. 2006[77] used non-UK value sets.[77, 99, 129, 130]

B.3.4.4. Adverse reactions

AE-related disutility was applied as a one-time QALY decrement in the first model cycle as summarised in Table 51. The disutility associated with AEs was calculated in each treatment arm as a function of: treatment specific AE risks, the mean duration of AEs per episode; the mean number of episodes per affected patient in KEYNOTE-091 (all summarised in Table 49) and the estimated disutility associated with an active grade 3+ AE based on analyses of EQ-5D-3L data from the KEYNOTE-091 trial (Table 51) . Information related to AE incidence/risk, duration and number of episodes can be found in Section B.2.10. Using KEYNOTE-091 data, the disutility of an active grade 3+ AE was calculated as the difference

between the mean utility across patient-visits in the disease-free state with any grade 3+ AE (0.736) minus the mean utility in the disease-free health state with no grade 3+ AE (0.852) as described in Table 50.

Table 51. Estimated AE disutility (total QALYs) for grade 3+ AEs (descriptive approach excl. grades 1-2 from DF)

	Descriptive estimated decrement		Source
	Mean	SE	
Disutility for grade 3+ AEs	-0.116	0.033	KEYNOTE-091 (Jan 2023 data cut-off)

Abbreviations: AE adverse event; DF: disease free

B.3.4.5. Age-related disutility

Within the model, age adjustment was applied in the base-case to account for general deterioration in HRQoL as a patient gets older. Age-related disutility was based on the formula from Ara and Brazier study as summarised in Table 52.[131]. This was applied within the model by use of the baseline age (64.3 years) and proportion female (31.7%).

Table 52 Age adjustment from Ara et al. (2010)[131]

Variable	Coefficient
Male (β1)	0.021213
Age (β1)	-0.000259
Age2 (β2)	-0.000033
Constant (β0)	0.950857

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

As described in Section B.3.1 an SLR was conducted (with the original SLR performed in 2021 and subsequently updated in 2022 and 2023) to identify published studies for evaluating cost-effectiveness, costs and resource use, and health-related quality of life for treatments in NSCLC relevant to the decision problem. As the SLR search strategy combined the cost-effectiveness, HRQoL and costs and healthcare resource use, full details on the methodology of the SLR, including search terms are summarised in Appendix G. Search results and PRISMA for costs and healthcare resource use are provided in detail in Appendix I. 13 cost and/or resource-use studies (reported in 16 publications) were identified as relevant for inclusion in the SLR. The study by Andreas et al. (2018) [59] was the only study which included UK costs and resource utilisation, though German and French HCRU were also included. The Andreas study (2018) was leveraged in the KEYNOTE-091 model to the extent that it had informed some of the parameters in TA761, which we re-used. The results of the SLR also found 7 studies (8 publications) were identified for the US[71, 132-138], 2

from Canada[139, 140], 2 from Italy [141, 142]and 1 from South Korea. [143] As these studies were not UK-based studies these were considered irrelevant for the economic model.

B.3.5.1. Intervention and comparators' costs and resource use

The Pembrolizumab dose in the adjuvant setting is consistent with the license (for SmPC see Appendix C) and the dosing regimen in the KEYNOTE-091 trial. In clinical practice, the option of Q6W dosing is also available (as described in the SmPC and provided in Appendix A). This alternative dosing regimen for pembrolizumab is popular in other adjuvant settings in the NHS and therefore is assessed in a scenario analysis. A PAS with a simple discount is currently in place for pembrolizumab, reported in Appendix K. Estimation of the cost of treatment is not inclusive of the relative dose intensity observed in the KEYNOTE-091 trial (Table 53) in the base-case with a limit on the portion of the ToT KM used as described in section B.3.3.3 however in scenario analysis RDI is included with no time limit applied to the KM.

As there are currently no active treatment options available for patients with NSCLC following successful resection and adjuvant chemotherapy, the current standard of care for these patients is routine surveillance, with no associated active therapy costs.

Table 53. Adjuvant pembrolizumab dosing regimen and relative dose intensity[65]

Adjuvant regimen	Dosing schedule description	Relative dose intensity (%)
Pembrolizumab	200 mg IV Q3W, up to 18 cycles	[redacted]
Pembrolizumab	400 mg IV Q6W, up to 9 cycles	[redacted]

Abbreviations: IV – Intravenous; Q3W – Once every 3 weeks

B.3.5.2. Health state unit costs and resource use

Unit drug costs for adjuvant chemotherapy regimens and subsequent treatments are summarised in Table 54. Dosing schedules and costs for comparator treatments were sourced from the relevant UK specific sources such as the British National Formulary (BNF) and the drugs and pharmaceutical electronic market information tool (eMIT).

Table 54. Unit drug costs for treatments in the adjuvant, local-regional recurrence, and/or distant metastases settings

Regimen or component	Strength per vial or tablet (mg)	Dosing schedule	List price per vial or pack (£)
Carboplatin	450	AUC 6 mg/ml/min IV Q3W, up to 4 cycles	£14.69
Cisplatin	50	75 mg/m2 IV Q3W, up to 4 cycles	£6.03
Osimertinib	80	80 mg orally once daily	£5,385*

Paclitaxel	300	200 mg/m2 IV Q3W, up to 6 cycles	£15.97
Pemetrexed	100	500 mg/m2 IV Q3W	£125

*MSD are do not know the PAS price of osimertinib so are arbitrarily assuming a 60% discount in all our analyses. This can be corrected by the EAG at a later date.

B.3.5.3. Administration costs

The cost of administration is sourced from the NHS Reference Costs using the SB12Z HRG code, the cost is presented in Table 55. This is in-line with previous Pembrolizumab appraisals (TA837[79], TA904[144])

Table 55. Administration costs

Administration type	Unit cost per administration (£)	Source
Simple parenteral chemotherapy, at first attendance	£287	2021/22 NHS Reference Cost, SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance

The EMA licence for pembrolizumab as monotherapy also allows treatment to be administered at half the frequency of the Q3W regimen (i.e., 6-weekly [Q6W]) and double the dose (i.e. 400mg), which may be preferred by patients and their treating clinicians due to the increased convenience of this regimen. The Q6W regimen would be expected to reduce the total administration costs accruing during the duration of pembrolizumab adjuvant therapy but is not reflected in the base-case.

B.3.5.4. Health state resource use and costs

The total per cycle cost for patients in the DF, LR and DM health states are summarised in Table 56. This was based on two previous NICE appraisals in NSCLC: primarily from the atezolizumab (TA823) appraisal and some resource use estimates from the osimertinib (TA761) appraisal with some modifications from our 2023 Clinical Advisory Board. Full details are provided in the respective NICE appraisals but are summarised as follows: in the atezolizumab appraisal, the resource use estimates associated with active monitoring was based on information obtained from UK oncologists. In the osimertinib appraisal, the HCRU estimates were originally based on both the Andreas et al, 2018 study and NICE TA654 appraisal [59, 145]. We listed the HCRU estimates from both appraisals and sought to validate these with clinical experts from MSD's 2023 Clinical Advisory Board. The experts commented that they preferred the approach from the atezolizumab appraisal except for hospitalisations, which were not costed in the atezolizumab appraisal, and the experts confirmed they would occur at broadly the frequency presented in the osimertinib appraisal.

[89]The exception to this was that the clinical experts considered the hospitalisation resource use in the DF health state to be 1 in every 2 years instead of 0.9 per year originally. Therefore, in the model we assumed this value to be 0.5 and subsequently converted this into a weekly resource use rate in keeping with the weekly cycle length in the model. All other resource use estimates from the atezolizumab appraisal [99] were also converted to weekly resource use rates.

Consistent with the TA823 approach[99], patients in either treatment arm receive the same total weekly per cycle cost. As there is a single DM health state in the model, we weighted the resource use estimates from the atezolizumab appraisal by the estimated time patients spend in DM1 and DM2 in each arm. This value is slightly different depending on I/O eligibility but, broadly, patients spend approximately 42% of their remaining LYs in DM1 and therefore 58% in DM2. A single resource use estimate for DM was then calculated for each resource use element. Unit costs were sourced from NHS reference costs 2021/22 [146]and PSSRU (2022). [147]

Table 56. healthcare resource use by DF and LR health states

Resource use element	Unit cost	DF up to year 5		DF years 5-7		DF years 7+		LRR		Reference
		%	Resource use	%	Resource use	%	Resource use	%	Resource use	
Hospitalisation	£2,879	100%	0.010	53%	0.010	5%	0.010	100%	0.030	DFS hospitalisation osimertinib (TA761) and MSD Clinical Advisory Board 2023. NHS reference costs 2021-22, DZ17L-V - Respiratory Neoplasms with CC Score 0-10+; Non-elective long and short stay (weighted average)
Outpatient visit	£205.78	100%	0.027	53%	0.027	5%	0.027	100%	0.091	Per visit. NHS Reference Costs 2021-22: Code 370 outpatient medical oncology
Community nurse	£96	100%	0.023	53%	0.023	5%	0.023	100%	0.038	Band 8b, Cost per hour nurse. Personal Social Service Research Unit in UK, 2023
Clinical nurse specialist	£96	100%	0.033	53%	0.033	5%	0.033	100%	0.163	Assumed same as community nurse cost
GP surgery consultation	£41	100%	0.054	53%	0.054	5%	0.054	100%	0.082	PSSRU unit costs 2022. With qualification cost, average consultation (9.22 minutes).
GP home visit	£123	100%	0	53%	0	5%	0	100%	0	PSSRU unit costs 2022. With qualification cost. Assume 3 times GP surgery unit cost.
Therapist visit	£50	100%	0	53%	0	5%	0	100%	0	PSSRU 2022 cost per hour for community occupational therapist (including qualifications)
CT chest scan	£142	100%	0	53%	0	5%	0.000	100%	0.032	NHS Reference Costs 2021-22, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)
Chest radiography	£38.28	100%	0.027	53%	0.027	5%	0.027	100%	0.023	Per visit. NHS Reference Costs 2021-22: DPAF
Electrocardio-gram	£181.14	100%	0	53%	0	5%	0	100%	0	NHS Reference Costs 2021-22, Electrocardiogram Monitoring or Stress Testing, EY51Z
Resource use cost per week cost		**£42**		**£22**		**£2**		**£133**		**Calculation (weighted average)**

Table 57. healthcare resource use by DM (pre-progression and post progression)

Resource use element	Unit cost	DM (pre-progression) One-time		DM (pre progression subsq treatment)		DM (post progression)		Reference
		%	Resource use	%	Resource use	%	Resource use	
Hospitalisation	£2,879	100%	0.05	100%	0.05	100%	0.05	DFS hospitalisation osimertinib (TA761) and MSD Clinical Advisory Board 2023. NHS reference costs 2021-22, DZ17L-V - Respiratory Neoplasms, with CC Score 0-10+; Non-elective long and short stay (weighted average)
Outpatient visit	£205.78	100%	0.18	100%	0.18	100%	0.15	Per visit. NHS Reference Costs 2021-22: Code 370 outpatient medical oncology
Community nurse	£96	100%	0.17	100%	0.17	100%	0.17	Band 8b, Cost per hour nurse. Personal Social Service Research Unit in UK, 2023
Clinical nurse specialist	£96	100%	0.23	100%	0.23	100%	0.23	Assumed same as community nurse cost
GP surgery consultation	£41	100%	0.23	100%	0.23	100%	0	PSSRU unit costs 2022. With qualification cost, average consultation (9.22 minutes).
GP home visit	£123	100%	0	100%	0	100%	0.50	PSSRU unit costs 2022. With qualification cost. Assume 3 times GP surgery unit cost.
Therapist visit	£50	100%	0	100%	0	100%	0.50	PSSRU 2022 cost per hour for community occupational therapist (including qualifications)
CT chest scan	£142	100%	0.08	100%	0.08	100%	0	NHS Reference Costs 2021-22, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)
Chest radiography	£38.28	100%	0.13	100%	0.13	100%	0.12	Per visit. NHS Reference Costs 2021-22: DPAF
Electrocardiogram	£181.14	100%	0.02	100%	0.02	100%	0.02	NHS Reference Costs 2021-22, Electrocardiogram Monitoring or Stress Testing, EY51Z
PET-CT scan	£722.11	100%	1	0%	NA	0%	N/A	NHS Reference Costs 2021/2022: RN01A/RN02A/RN03A - Positron Emission Tomography with Computed Tomography (PET-CT) of one/two or three/more than three areas, 19 years and over (weighted average)
MRI	£322.35	100%	1	0%	NA	0%	N/A	NHS Reference Costs 2021/2022: RD05Z - Magnetic Resonance Imaging Scan of more than three areas, with contrast (Imaging: Outpatient)
Resource use		**£1,299 one-time**		**£254 per week**		**£313 per week**		**Calculation (weighted average)**

As in the previous appraisals, a one-time cost was also applied to all patients transitioning into the DM state from anywhere. This reflects routine appointments and scans that a patient would receive upon diagnosis of distant metastasis (e.g. PET-CT to assess the extent of disease) and was confirmed as appropriate by clinicians at the 2023 advisory board.

Local-regional recurrence health state entry costs

In addition to the total health state per cycle costs, patients receive a one-time treatment cost related to local-regional recurrence of their cancer on entry into the LR state as summarised in Table 58. The proportions listed represent the proportion of patients that receive the respective resource use element, mostly radiotherapy-based treatments. These proportions were elicited at the 2022 Clinical Advisory Board. Clinicians also advised us that in UK practice some patients would get durvalumab after chemo-radiotherapy. We decided to exclude this from our economic model for several reasons: it would only relate to a specific subset of patients (unresectable stage III PDL1>1%), the generalisability of the pivotal trial is uncertain in a resected-and-recurred population, and it would be very complex to implement in an intermediate health state in a Markov cohort model such as this. We note this is a limitation but, given that it only applies to a subset of patients and that the committee's preferred scenarios in the FAD for TA798 were "between £20,000 and £30,000/QALY", and the implied additional Net Health Benefit is therefore small, we feel that excluding it is unlikely to meaningfully bias the analysis.

Table 58 One-time treatment costs in the local-regional recurrence health state

Resource use element in LR state	% of patients	Unit cost	Notes and unit cost source
Salvage surgery	2%	£11,273	NHS reference costs 2021/22: DZ02H-K, Complex Thoracic Procedures, 19 years and over, with CC Score 6+ CC Score 0 to 6+ (weighted average)
CRT radiotherapy component	30%	£4,376*	Costed as hyper fractionated RT based on NG122 resource use and NHS reference costs. (see B.3.5.7)
RT	20%	£7,328*	Lung cancer update, NICE guideline NG122 (2019). [148]Average of 3 types of radiotherapy: CHART, hyper fractionated and standard fractionated (p114-116). (see B.3.5.7)
Systemic therapy (chemotherapy alone).	30%	£2,588	Costed as vinorelbine + cisplatin (6.9 cycles in KN091). This cost is also added as the chemotherapy component of CRT.

BSC	18%	£0	Assume zero cost

Abbreviations: BSC; Best supportive care; CRT: chemoradiotherapy; LR: local-regional recurrence; PDC: platinum doublet chemotherapy; RT: radiotherapy. NOTE: *a weighted average of these two costs is applied in the model as a single RT cost upon transition to LR.

B.3.5.5. Subsequent treatment costs in the distant metastases state

Drug acquisition and administration costs for subsequent treatment in DM state

The drug acquisition and administration costs associated with the subsequent systemic therapies were also considered in the model, specifically for first- and second-line therapies. The acquisition and administration costs are applied as a one-time cost when patients enter the distant metastases state. Patients who entered the distant metastases state were assumed to receive first-line treatment for metastatic NSCLC. The treatments received and by what proportion patients receive in first-line metastatic treatment is determined by I/O eligibility status as fully described in B.3.3.2. As also described in B.3.3.2, subsequent treatment market shares for second-line metastatic treatment were assumed to be the same irrespective of I/O eligibility or original adjuvant treatment received.

The drug acquisition cost per administration is based on unit drug costs (as already summarised in Table 54) and defined dosing schedules as shown in Table 59. The dosing schedules and stopping rules were based on prescribing information and the design of the pivotal trials. For simplicity, consistency and dynamism within the mode, times on treatment were assumed to be equal to PFS on the drug as derived within the model (section B.3.3.2).

Table 59. Dosing schedules for first-line and second-line therapies for metastatic NSCLC

Regimen	Drug component	Dosing schedule	Maximum ToT (weeks)	% receiving specific drug component or dosing schedule	Sources
First-line therapies					
Osimertinib	Osimertinib	80 mg orally once daily	No max	100.0%	Prescribing information, Tagrisso (osimertinib)[149]
Carboplatin + (nab-)paclitaxel (SQ)	Carboplatin	AUC 6 mg/ml/min IV Q3W, up to 4 cycles	12	100.0%	Paz-Ares et al. (2018)[150] [KEYNOTE-407] (1L trial)
	Paclitaxel	200 mg/m2 IV Q3W, up to 4 cycles	12	59.6%	
	Nab-paclitaxel	100 mg/m2 IV on days 1, 8, and 15 Q3W, up to 4 cycles	12	40.4%	
Pembrolizumab + carboplatin + (nab-)paclitaxel	Pembrolizumab (Q3W)	200 mg IV Q3W, up to 24 months	104	100.0%	Paz-Ares et al. (2018)[150] [KEYNOTE-407] (1L trial)
	Pembrolizumab (Q6W)	400 mg IV Q6W, up to 24 months	104	0.0%	
	Carboplatin	AUC 6 mg/ml/min IV Q3W, up to 4 cycles	12	100.0%	
	Paclitaxel	200 mg/m2 IV Q3W, up to 4 cycles	12	60.8%	
	Nab-paclitaxel	100 mg/m2 IV on days 1, 8, and 15 Q3W, up to 4 cycles	12	39.2%	
Pembrolizumab + pemetrexed + platinum	Pembrolizumab (Q3W)	200 mg IV Q3W, up to 24 months	104	100.0%	Gandhi et al. (2018)[151] & Gadgeel et al. (2020)[152] [KEYNOTE-189]
	Pembrolizumab (Q6W)	400 mg IV Q6W, up to 24 months	104	0.0%	
	Pemetrexed	500 mg/m2 IV Q3W	No max	100.0%	
	Carboplatin	AUC 5 mg/ml/min IV Q3W, up to 4 cycles	12	72.6%	

	Cisplatin	75 mg/m2 IV Q3W, up to 4 cycles	12	27.4%	
Pemetrexed + platinum	Pemetrexed	500 mg/m2 IV Q3W	No max	100.0%	Gandhi et al. (2018)[151] & Gadgeel et al. (2020)[152] [KEYNOTE-189]
	Carboplatin	AUC 5 mg/ml/min IV Q3W, up to 4 cycles	12	71.8%	
	Cisplatin	75 mg/m2 IV Q3W, up to 4 cycles	12	28.2%	
Second-line therapies					
Docetaxel	Docetaxel	75 mg/m2 IV Q3W	No max	100.0%	Prescribing information, Taxotere (docetaxel)[153]; Fossella et al. (2000)[154] [TAX 320]
Pemetrexed + platinum	Pemetrexed	500 mg/m2 IV Q3W	No max	100.0%	Gandhi et al. (2018)[151] & Gadgeel et al. (2020)[152] [KEYNOTE-189]
	Carboplatin	AUC 5 mg/ml/min IV Q3W, up to 4 cycles	12	71.8%	
	Cisplatin	75 mg/m2 IV Q3W, up to 4 cycles	12	28.2%	

Abbreviations: IV, intravenous; NSCLC, non-small cell lung cancer; NSQ, non-squamous; Q#W, once every # weeks; SQ, squamous; ToT, time on treatment.

Time on treatment for subsequent therapies

The durations for first-line metastatic treatments were modelled using the exponential rates of PFS failure, which were used to estimate the treatment discontinuation rates as already described in Table 41. For second-line treatments, mean treatment durations were based on empirical estimates from n=9,121 patients from the Flatiron database [155]as summarised in Table 60. This cohort comprised of adults who were previously treated with first-line systemic anti-cancer therapy (I/O monotherapy, I/O combination, chemotherapy, and/or targeted therapies) for advanced or metastatic NSCLC (unresectable stages IIIB, IIIC, or stage IV) who initiated second-line treatment. Flatiron was selected as this is a cancer-focused longitudinal database comprising of de-identified patient-level data from 280 cancer clinics in the US (~800 sites of care) further details can be found in Appendix P. The mean days on each second-line treatment was converted to weekly ToT consistent with the weekly cycles applied in the model. The model estimated the mean total cost of each first- and second-line treatment regimen over the expected duration of each therapy. The mean costs of first- and second-line treatment were then calculated for each adjuvant treatment arm as a weighted average based on the first- and second-line market shares within each adjuvant treatment arm.

Table 60. Time on treatment for Second-line Treatment Regimens

Second-line treatment regimen	Component	ToT (weeks)
		Mean
Docetaxel	Docetaxel	8.757
Pemetrexed + platinum	Pemetrexed	15.371
	Carboplatin	8.243
	Cisplatin	7.714

Abbreviations:ToT: time on treatment. Sources for mean ToT: Flatiron database (data cutoff date: May 2023); Flatiron database (data cutoff date: Nov 2021; see Appendix P for methodology)

B.3.5.6. Adverse reaction unit costs and resource use

The costs of grade 3+ with ≥1% frequency in pembrolizumab and placebo are summarised in Table 61. As outlined in Section B.3.4.4 and in line with previous NICE appraisals, costs associated with AEs were applied at model entry. In each model arm, this lump-sum cost was calculated as the sum-product of AE risks, mean number of episodes per patient with the AE (Table 49), and mean cost per episode of the AE (adjusting for proportions with and without hospitalisations)(Table 61). Unit costs for each event were sourced from the most recent (2021/22) NHS reference costs and are consistent with previous appraisals in NSCLC. For costs that did not result in hospitalisation £160 was applied which is the cost of a clinical oncology outpatient attendance (code 800) in the NHS reference costs 2021/22.

Table 61. Cost per grade 3+ adverse event

Grade 3-5 AEs	Cost per event (with hospitalisation)	Source
Diarrhoea	£230	NHS Reference Cost 2021/22, FD10: Non-Malignant Gastrointestinal Tract Disorders - Regular Day or Night Admissions (weighted average)
Dyspnoea	£589	NHS Reference Cost 2021/22, DZ19: Other Respiratory Disorders - Regular Day or Night Admissions (weighted average)
Hypertension	£193	NHS Reference Cost 2021/22, EB04Z: Hypertension - Regular Day or Night Admissions
Hyponatraemia	£238	NHS Reference Cost 2021/22, WH13: Abnormal Findings without Diagnosis - Regular Day or Night Admissions (weighted average)
Pneumonia	£1,916	NHS Reference Costs 2021/2022 [DZ11T Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9].[106]
Pneumonitis	£1,916	Assume same cost as Pneumonia
Weight increased	£0	Reference: CTCAE guidelines. Assume zero cost (investigation)

Abbreviations: AE: adverse events; CTCAE; Common Terminology Criteria for Adverse Events

B.3.5.7. Miscellaneous unit costs and resource use

The cost of a PD-L1 test (£40.50 source: NICE TA823) was divided by the prevalence of PDL1<50% in the KEYNOTE-091 trial (72%) to determine the testing costs required to identify an eligible patient added to all patients in the pembrolizumab arm of the model.

The cost of radiotherapy was calculated by a weighted average of the cost of CRT, continuous hyper fractionated accelerated radiotherapy (CHART), hyper fractionated accelerated radiotherapy and standard fractionated therapy and is summarised in Table 62. Each type of radiotherapy was calculated separately by way of a weighted average of the number of resource use units i.e. defining volume, delivering fraction (both complex and non-complex) and hospital inpatient days. Hospital inpatient days were only applied to CHART consistent with the approach in NG122.[148] These resource use estimates were sourced from the NG122, Evidence Review B. The total cost of each type of radiotherapy was then weighted by the proportion of patients receiving radiotherapy once they enter the LRR health state, which was informed by the 2022 Clinical Advisory Board. As summarised in Table 58, 30% of patients receive CRT and 20% receive radiotherapy. We divided this remaining 20% by 3 to assign an equal proportion for CHART, standard fractionated and hyper fractionated

accelerated radiotherapy. Unit costs were also sourced from NG122 and updated to current NHS reference costs.[146]

Table 62. Average Cost of Radiotherapy

Resource use	Resource use units	Cost	Source
CHART			
Define volume for simple radiation therapy with imaging and dosimetry	1	£790	Unit cost from NHS National Schedule of Reference Cost 2021/22 – SC45Z Resource use from CG121
Deliver a fraction of complex treatment on a megavoltage machine	1	£212	Unit cost from NHS National Schedule of Reference Cost 2021/22 - SC23Z Resource use from CG121
Deliver a fraction of treatment on a megavoltage machine	35	£178	Unit cost from NHS National Schedule of Reference Cost 2021/22 – SC22Z Resource use from CG121
Number of days of hospital inpatient stay	12	£4,239	NG122 cost inflated from 2017-2022 using CPI (2017 costs first 5 days - £1,590 + 7 Excess bed days (£313) Resource use from NG122
Total cost of CHART		**£11,458**	Calculation (weighted average)
Hyper fractionated accelerated radiotherapy			
Define volume for simple radiation therapy with imaging and dosimetry	1	£790	Unit cost from NHS National Schedule of Reference Cost 2021/22 – SC45Z Resource use from CG121
Deliver a fraction of complex treatment on a megavoltage machine	1	£212	Unit cost from NHS National Schedule of Reference Cost 2021/22 – SC23Z Resource use from CG121
Deliver a fraction of treatment on a megavoltage machine	19	178	Unit cost from NHS National Schedule of Reference Cost 2021/22 - SC22Z Resource use from CG121
Total cost of hyper fractionated accelerated radiotherapy		**£4,376**	Calculation (weighted average)
Standard fractionated radiotherapy			
Define volume for simple radiation therapy with imaging and dosimetry	1	£790	Unit cost from NHS National Schedule of Reference Cost 2021/22 -SC45Z Resource use from CG121

Deliver a fraction of complex treatment on a megavoltage machine	1	£212	Unit cost from NHS National Schedule of Reference Cost 2021/22 - SC23Z Resource use from CG121
Deliver a fraction of treatment on a megavoltage machine	29	£178	Unit cost from NHS National Schedule of Reference Cost 2021/22 -SC22Z Resource use from CG121
Total cost of standard fractionated radiotherapy		**£6,152**	Calculation (weighted average)
Total radiotherapy cost for use in the model		**£5,557**	Weighted average with proportions informed by 2022 Clinical Advisory Board[45]

Terminal care costs

A one-time terminal care cost is applied on movement to death (£7,429). This is inflated to the current cost year from the original value of £6,207. This was sourced from the Georghiou and Bardsley (2014) study [156] and has been used and accepted in a number of pembrolizumab appraisals (TA766[81], TA801[157], TA830[82], TA837[79], TA904 [144]) which have been accepted by the NICE Committee.

B.3.6. Severity

MSD does not believe this indication qualifies for a Severity Modifier as expected QALY loss on SoC vs. the general population does not meet any Severity Modifier threshold.

B.3.7. Summary of base-case analysis inputs and assumptions

B.3.7.1. Summary of base-case analysis inputs

The base-case inputs included in the KEYNOTE-091 model are summarised in Table 63.

Table 63. Summary of variables applied in the economic model

Variable	Value	SE	Distribution for PSA	Section in submission
Cycle length	1 week	-	Not varied	B.3.2.2
Time horizon, years	35.7 years	-	Not varied	
Discount rate: Costs	3.5%	-	Not varied	
Discount rate: Outcomes	3.5%	-	Not varied	
Starting age, years	64.3 years	-	Not varied	B.3.2.1
Female, %	31.7%	-	Not varied	
Body surface area, m2	1.9	(0.00583)	Normal	
Weight, kg	74.8	(0.46054)	Normal	

Squamous histology (%) pembrolizumab	27.8%	-	Not varied	
Non-squamous histology (%) pembrolizumab	72.2%	-	Not varied	
Glomerular filtration rate (GFR) (mL/min/1.73 m2)	75	-	Not varied	
Pembrolizumab				
Parameter estimates for DF→LR	Log-normal		Multivariate normal	B.3.3.1
Parameter A	6.6121	(0.2314)	Multivariate normal	
Parameter B	1.7913	(0.1758)	Multivariate normal	
Parameter C	-	-	Multivariate normal	
Parameter estimates for DF→DM	Log-normal		Multivariate normal	
Parameter A	6.8200	(0.2660)	Multivariate normal	
Parameter B	2.4393	(0.2113)	Multivariate normal	
Parameter C	-	-	Multivariate normal	
Parameter estimates for DF→death	Exponential		Multivariate normal	
Parameter A	0.00045	(0.0001)	Multivariate normal	
Parameter B	-	-	Multivariate normal	
Parameter C	-	-	Multivariate normal	
Placebo				
Parameter estimates for DF→LR	Log-normal		Multivariate normal	B.3.3.1
Parameter A	6.3130	(0.2098)	Multivariate normal	
Parameter B	1.7448	(0.1638)	Multivariate normal	
Parameter C	-	-	Multivariate normal	
Parameter estimates for DF→DM	Log-normal		Multivariate normal	
Parameter A	6.1717	(0.2162)	Multivariate normal	
Parameter B	2.4398	(0.1844)	Multivariate normal	

Parameter C		-	-	Multivariate normal	
Parameter estimates for DF→death		Exponential		Multivariate normal	
Parameter A		0.0003899	(0.0001)	Multivariate normal	
Parameter B		-	-	Multivariate normal	
Parameter C		-	-	Multivariate normal	
Parameters for cure point					
Start of cure period, year		5	-	Not varied	B.3.3.1
End of cure period, year		7	-	Not varied	
Maximum risk reduction, %		95%	-	Not varied	
Calibration					
Calibration cap		5-7 years	-	Not varied	B.3.3.2
SEER adjustment factor		0.70172	-	Not varied	B.3.3.2
Exponential rates of LR to DM (calibrated, before cap)					
Pembrolizumab		0.0043	(0.0009)	Normal	B.3.3.2
Placebo		0.0064	(0.0013)	Normal	
Exponential rates of LR to death (calibrated, before cap)					
Pembrolizumab		0.0013	(0.0004)	Normal	B.3.3.2
Placebo		0.0019	(0.0003)	Normal	
Subsequent treatment market shares (I/O eligibility status and adjuvant) – first-line					
Pembrolizumab I/O-eligible (1L)	Osimertinib	15%	-	Not varied	B.3.3.2
	Pembrolizumab + carboplatin + paclitaxel	32.6%	-		
	Pembrolizumab + pemetrexed + platinum	52.4%	-		
	Carboplatin + paclitaxel	0%	-		
	Pemetrexed + platinum (PDC)	0%	-		
Pembrolizumab I/O-ineligible (1L)	Osimertinib	15%	-	Not varied	
	Pembrolizumab + carboplatin + paclitaxel	0%	-		
	Pembrolizumab + pemetrexed + platinum	0%	-		
	Carboplatin + paclitaxel	32.6%	-		
	Pemetrexed + platinum (PDC)	52.4%	-		
	Osimertinib	15%	-	Not varied	

Active monitoring - I/O-eligible (1L)	Pembrolizumab + carboplatin + paclitaxel	32.6%	-		
	Pembrolizumab + pemetrexed + platinum	52.4%	-		
	Carboplatin + paclitaxel	0%	-		
	Pemetrexed + platinum (PDC)	0%	-		
Subsequent treatment market shares (I/O eligibility status and adjuvant) – second-line					
Pembrolizumab I/O-eligible (2L)	Docetaxel	30%	-	Not varied	B.3.3.2
	Pemetrexed + platinum	30%	-		
	No active treatment (BSC)	40%	-		
Pembrolizumab I/O-ineligible (2L)	Docetaxel	30%	-	Not varied	
	Pemetrexed + platinum	30%	-		
	No active treatment (BSC)	40%	-		
Active monitoring - I/O-eligible (1L)	Docetaxel	30%	-	Not varied	
	Pemetrexed + platinum	30%	-		
	No active treatment (BSC)	40%	-		
Exponential rates and HRs of OS and PFS failure by 1L DM treatment					
Exponential rate of death in DM state					
Pembrolizumab + pemetrexed + platinum non-sq PD-L1 < 50% NSCLC		0.0081	(0.0007)	Normal	B.3.3.2
Pembrolizumab + carboplatin + paclitaxel sq PD-L1 < 50% NSCLC		0.0097	(0.0008)	Normal	
Osimertinib EGFR+ NSCLC (assumed efficacy for proportion on targeted therapy)		0.0041	(0.0002)	Normal	
Pemetrexed + platinum non-sq PD-L1 < 50% NSCLC		1.69	(0.12)	Normal	
Carboplatin + paclitaxel sq PD-L1 < 50% NSCLC		1.41	(0.11)	Normal	
Exponential rate of death or progression in DM state					
Pembrolizumab + pemetrexed + platinum non-sq PD-L1 < 50% NSCLC		0.0197	(0.0015)	Normal	B.3.3.2
Pembrolizumab + carboplatin + paclitaxel sq PD-L1 < 50% NSCLC		0.0245	(0.0018)	Normal	
Osimertinib EGFR+ NSCLC (assumed efficacy for proportion on targeted therapy)		0.0084	(0.0008)	Normal	
Pemetrexed + platinum non-sq PD-L1 < 50% NSCLC		1.59	(0.12)	Normal	

Carboplatin + paclitaxel sq PD-L1 < 50% NSCLC	1.54	(0.11)	Normal	
Medical management costs by health state				
Medical management costs in DF state per week, up to year 5	£42	(£87)	Gamma	B.3.5.4
Medical management costs in DF state per week, years 5-7	£22	(£78)	Gamma	
Medical management costs in DF state per week, years 7 onward	£2	(£71)	Gamma	
Salvage surgery costs upon LR state entry (one-time cost)	£225	(£772)	Gamma	
Radiotherapy costs upon LR state entry (one-time cost)	£3,823	(£1,270)	Gamma	
Medical management costs in LR state (per week)	£133	(£179)	Gamma	
Medical management costs upon DM state entry (one-time cost)	£1,299	(£216)	Gamma	
Medical management costs in pre-progression DM state (per week)	£254	(£216)	Gamma	
Medical management costs in post-progression DM state (per week)	£313	(£220)	Gamma	
Terminal care cost (one-time cost)	£7,429	(£2,655)	Gamma	B.3.5.7
Drug administration costs				
IV (simple)	£287	(£26.43)	Gamma	B.3.5.3
IV (complex)	£354	(£6)	Gamma	
IV (subsequent)	£368	(£13)	Gamma	
Oral	£0	(£0)	Gamma	
AE costs				
Pembrolizumab	£103	(£169.77)	Gamma	B.3.5.6
Placebo	£66	(97.26)	Gamma	
Utilities				
Utility of DF (without toxicity)	0.852	(0.012)	Beta	B.3.4.1
Utility of LR	0.776	(0.026)	Beta	
Utility of pre-progression DM	0.743	(0.022)	Beta	
Utility of post-progression DM	0.668	(0.0198)	Beta	
Disutility from AEs	-0.11600	(0.0384)	Normal	
Disutility associated with age	-0.00026	(0.00005)	Normal	
Disutility associated with age2	-0.00003	(0.00001)	Normal	
Utility associated with male gender	0.02121	(0.00424)	Normal	

Abbreviations: AE, adverse event; DM, distant metastases; DF, disease-free; LR, local-regional recurrence; PSA, probabilistic sensitivity analysis; SE, standard error; sq; squamous

B.3.8. Base-case results

B.3.8.1. Base-case incremental cost-effectiveness analysis results

Table 64. Base-case results

Technologies	Total costs (£)	Total QALYs	Total LYs	Incremental costs (£)	Incremental QALYs	Incremental LYs	ICER vs. comparator (£/QALY)
Pembrolizumab	[redacted]	[redacted]	9.08	-	-	-	-
Placebo	[redacted]	[redacted]	7.98	[redacted]	0.92	1.10	[redacted]

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

Table 65. Disaggregated Base-case results

Costs (£)	Pembrolizumab	Placebo	Incremental (Pembrolizumab vs. Placebo)
Costs, total and by category	[redacted]	[redacted]	[redacted]
Adjuvant treatment costs	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in LR state	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Radiotherapy costs	[redacted]	[redacted]	[redacted]
Salvage surgery costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in DM state	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Costs, total and by state	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Death (one-time terminal care costs)	[redacted]	[redacted]	[redacted]

Effectiveness	**Pembrolizumab**	**Placebo**	**Incremental (Pembrolizumab vs. Placebo)**
Quality-adjusted life years (QALYs), total and by state	[redacted]	[redacted]	**0.92**
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
AE-related disutility	[redacted]	[redacted]	[redacted]
Age-related disutility	[redacted]	[redacted]	[redacted]
Life years (LYs), total and by state	**9.08**	**7.98**	**1.10**
Disease-free	7.10	5.89	1.21
Local-regional recurrence	0.63	0.54	0.09
Distant metastases	1.35	1.55	-0.20
Incremental outcomes (adjuvant pembrolizumab vs. comparator)	**Pembrolizumab**	**Placebo**	**Incremental (Pembrolizumab vs. Placebo)**
Incremental costs (£)	-	-	[redacted]
Incremental QALYs	-	-	0.92
Incremental LYs	-	-	1.10
Incremental costs per QALY gained	-	-	[redacted]
Incremental costs per LY gained	-	-	[redacted]

B.3.9. Exploring uncertainty

We conducted a range of sensitivity and scenario analyses on the model.

B.3.9.1. Probabilistic sensitivity analysis

Key parameters were varied within appropriate probability distributions to examine the effect of joint uncertainty on the model's results. The incremental costs and QALYs were similar to the deterministic base-case.

Table 66: PSA Results, Mean of 1,000 iterations

Average Δcosts	[redacted]
Average ΔQALYs	0.89
Average ICER (£/QALY)	[redacted]
Willingness-to-pay (£/QALY)	[redacted]
% cost-effective at WTP of £30,000	[redacted]

Figure 19: PSA scatterplot based on 1,000 model iterations

[redacted]

B.3.9.2. Deterministic sensitivity analysis

Figure 20 shows a tornado diagram in which key input parameters are varied to extreme values to examine their effect on the results.

Figure 20. Tornado diagram (DSA results)

[redacted]

B.3.9.3. Scenario analysis

We investigated a range of scenario analyses, which are outlined in Table 67.

Table 67. List of scenario analyses and justifications

No	Scenario	Justification
1	Cure point 5 years	Alternative cure assumptions.
2	Cure point 5-10 years	Alternative cure assumptions.
3	Calibration cap 6-8 years	Alternative cure assumptions.
4	Calibration removed entirely	Alternative calibration options.
5	Calibration removed, SEER adjustment added	Alternative calibration options.
6	Calibration without SEER adjustment	Alternative calibration options.
7	Pembrolizumab given Q6W	May be used in NHS practice.
8	Exponential/log-normal DFS curves	Alternate options in final curve selection process.
9	Weibull/log-normal DFS curves	Alternate options in final curve selection process.
10	Log-logistic/log-normal DFS curves	Alternate options in final curve selection process.
11	Gamma/log-normal DFS curves	Alternate options in final curve selection process.
12	Approach #2 Gompertz/Weibull DFS curves	Best fitting Approach #2 model by MSE to pembro arm
13	Approach #3 Exponential/Exponential DFS Curves	Best fitting Approach #3 model by MSE to pembro arm
14	20% of DM patients on no active treatment	Conservative analysis.
15	DF utilities including g1-2- AEs	Include more of short term observed data
16	G3+ AE disutilities excluded	Examine importance on ICER.
17	100% cure assumption	Also plausible.
18	RDI included with full KM	Examine effect on ICER.

Table 68. results of scenario analyses and justifications

Scenario Number	Scenario	Incremental costs (£)	Incremental QALYs	Incremental LYs	ICER vs. comparator (£/QALY)
	Base-Case	[redacted]	0.92	1.10	[redacted]
1	Cure point 5 years	[redacted]	0.93	1.10	[redacted]
2	Cure point 5-10 years	[redacted]	0.91	1.08	[redacted]

3	Calibration cap 6-8 years	[redacted]	0.96	1.16	[redacted]
4	Calibration removed entirely	[redacted]	0.71	0.80	[redacted]
5	Calibration removed, SEER adjustment added	[redacted]	0.62	0.67	[redacted]
6	Calibration without SEER-Medicare adjustment	[redacted]	0.92	1.09	[redacted]
7	Pembrolizumab given Q6W	[redacted]	0.92	1.10	[redacted]
8	Exponential/log-normal DFS curves	[redacted]	0.92	1.10	[redacted]
9	Weibull/log-normal DFS curves	[redacted]	0.88	1.05	[redacted]
10	Log-logistic/log-normal DFS curves	[redacted]	0.91	1.09	[redacted]
11	Gamma/log-normal DFS curves	[redacted]	0.90	1.07	[redacted]
12	Approach #2 Gompertz/Weibull DFS curves	[redacted]	0.98	1.17	[redacted]
13	Approach #3 Exponential/Exponential DFS Curves	[redacted]	1.18	1.41	[redacted]
14	20% of DM patients on no active treatment	[redacted]	0.96	1.16	[redacted]
15	DF utilities including g1-2 Aes	[redacted]	0.86	1.10	[redacted]
16	G3+ AE disutilities excluded	[redacted]	0.92	1.10	[redacted]
17	100% cure assumption	[redacted]	0.92	1.10	[redacted]
18	RDI included with full KM	[redacted]	0.92	1.10	[redacted]

B.3.10. Subgroup analysis

No subgroup analyses were conducted.

B.3.11. Benefits not captured in the QALY calculation

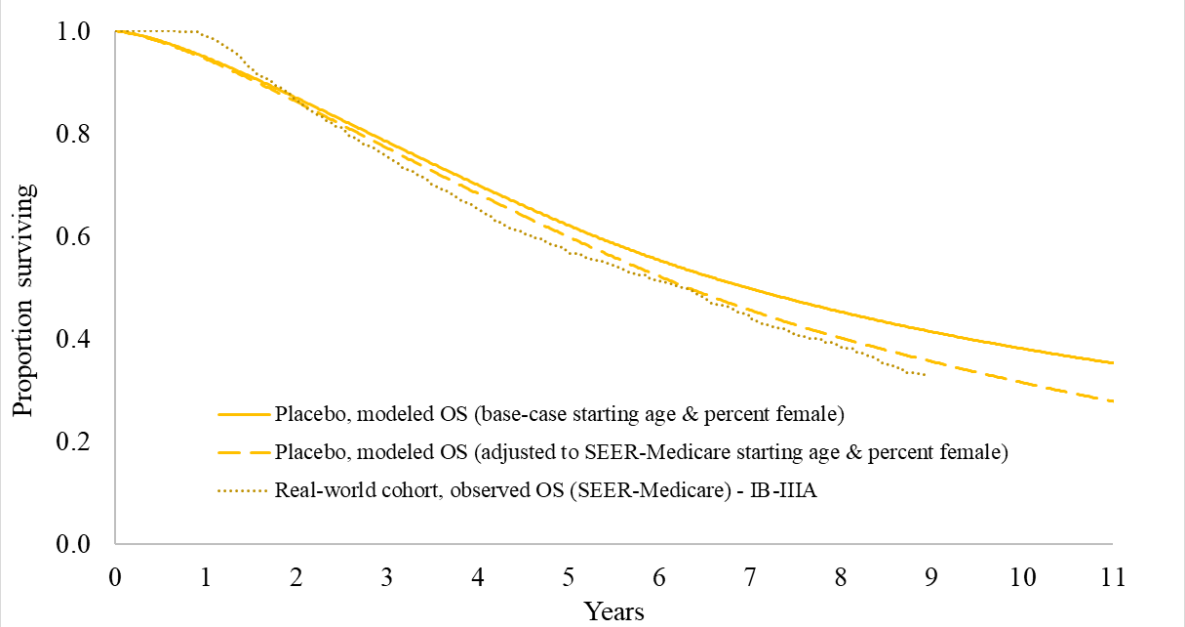
We were unable to identify any additional evidence on this although would highlight that delaying recurrences and increasing the cure rate among patients receiving radical treatment for NSCLC is likely to accrue QALY benefits to the patient's family and any dependents they may have, perhaps far into the future.

B.3.12. Validation

B.3.12.1. Validation of cost-effectiveness analysis

We compared the overall survival predictions from the placebo arm of the economic model to observed real-world data from SEER (e.g. Figure 15 in B.3.3.2). The model slightly overpredicted OS but this was likely due to the SEER data including patients with a mean age 9 years older. Increasing the starting age of patients in the control arm in the model moves the OS curve downwards into line with observed data (see Figure 21 below). The model also produces DFS and OS benefits which were in line with the clinical advice we received at the 2023 advisory board. The model's assumptions and inputs were discussed with two advisory boards comprising a total of 12 unique clinicians treating early NSCLC in the NHS. Overall we concluded that the model reasonably accurately characterised outcomes for patients with resected NSCLC on SoC and with the addition of adjuvant pembrolizumab.

Figure 21: Modelled placebo OS compared with Real-world Evidence from SEER



B.3.13. Interpretation and conclusions of economic evidence

The economic model shows that pembrolizumab principally accrues QALYs by delaying and preventing patients from progressing to the LR and DM health states in the model. As the LR and DM health states are much more costly than the DF health state, both in terms of background resource use and high-cost treatments, the initial

costs of pembrolizumab are to some extent offset by delaying and preventing patients progressing.

ICERs in the base-case and most scenario analyses were within NICE's usual cost-effectiveness threshold of £20,000-£30,000/QALY gained suggesting that pembrolizumab is a cost-effective addition to standard care. The probabilistic results were very similar to the deterministic results. In no scenarios was the ICER for pembrolizumab above £30,000/QALY gained. Of note, the scenario in which pembrolizumab is given every 6 weeks instead of every 3, which clinicians have told us likely reflects the way it will be used in NHS clinical practice, decreased the ICER due to reduced administration costs.

There were some uncertainties in the economic model. While it predicted observed OS in the placebo arm well, the model consistently underpredicted OS in the pembrolizumab arm. This observed phenomenon was not well explained by additional investigation of the clinical trial database although there was some scientific rationale for temporary calibrating the model to ensure it reproduced observed OS. However, pembrolizumab was still cost-effective in the scenario in which calibration was removed from the model.

The model also made a series of simplifying assumptions about downstream treatments and transition probabilities although it is not obvious that this would have biased the model in any particular direction.

B.4. References

1. National Institute for Health and Care Excellence (NICE). ID6220 - Durvalumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11197.
2. National Institute for Health and Care Excellence (NICE). TA823 Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta823 . 2022.
3. National Institute for Health and Care Excellence (NICE). TA761 Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection. Available from: https://www.nice.org.uk/guidance/ta761. 2022.
4. Medicines & Healthcare products Regulatory Agency (MHRA). KEYTRUDA® Summary of Product Characteristics. Available from: https://products.mhra.gov.uk/search/?search=keytruda&page=1 [Access Date: 21 February 2024].
5. European Medicines Agency (EMA). EMEA/H/C/003820/II/0121. Keytruda European Public Assessment Report (EPAR). Available from: https://www.ema.europa.eu/documents/variation-report/keytruda-h-c-003820-ii-0121-epar-assessment-report-variation_en.pdf. . 2023.
6. Cancer Research UK. Lung cancer. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/about. [Access Date: 25 February 2024] [
7. National Cancer Institute (NIH). Non-Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version. Available from: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#_4. [Access Date: 25 February 2024] [
8. National Lung Cancer Audit (NLCA). NLCA annual report (for the audit period 2018). Available from: https://www.hqip.org.uk/resource/national-lung-cancer-audit-annual-report-for-the-audit-period-2018/. [Access Date: 05 March 2024]. 2021.
9. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol. 2015;10(9):1243-60.
10. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011;6(2):244-85.
11. Duma N, Santana-Davila R, Molina JR. Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment. Mayo Clin Proc. 2019;94(8):1623-40.
12. National Institute for Health and Care Excellence (NICE). NICE guideline [NG122]. Lung cancer: diagnosis and management. Full guideline (2011). Last updated: 26 July 2023. Available from: https://www.nice.org.uk/guidance/ng122/evidence/full-guideline-pdf-6722113502. 2023.
13. Tsim S, O'Dowd CA, Milroy R, Davidson S. Staging of non-small cell lung cancer (NSCLC): a review. Respir Med. 2010;104(12):1767-74.

14. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. Chest. 2017;151(1):193-203.
15. Lababede O, Meziane MA. The Eighth Edition of TNM Staging of Lung Cancer: Reference Chart and Diagrams. Oncologist. 2018;23(7):844-8.
16. Mirsadraee S, Oswal D, Alizadeh Y, Caulo A, van Beek E, Jr. The 7th lung cancer TNM classification and staging system: Review of the changes and implications. World J Radiol. 2012;4(4):128-34.
17. Cancer Research UK. Stages and grades of lung cancer. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/stages-grades. [Access Date: 25 February 2024].
18. Sugimura H, Nichols FC, Yang P, Allen MS, Cassivi SD, Deschamps C, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. Ann Thorac Surg. 2007;83(2):409-17; discussioin 17-8.
19. Birring SS, Peake MD. Symptoms and the early diagnosis of lung cancer. Thorax. 2005;60(4):268-9.
20. National Cancer Institute (NIH). Non-Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version, Clinical Presentation. Available from: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#_48567_toc. [Access Date: 10 October 2023] [
21. World Health Organization (WHO). Cancer. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer. [Access Date: 25 February 2024].
22. International Agency for Research on Cancer (IARC). Cancer Today, Cancer Fact Sheets. Available from: https://gco.iarc.fr/today/fact-sheets-cancers. [Access Date: 25 February 2024] [
23. Cancer Research UK. Cancer incidence statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence [Access Date: 25 February 2024].
24. National Lung Cancer Audit (NLCA). National Lung Cancer Audit (NLCA) – State of the nation report 2023 for patients in England during 2021 and Wales during 2020-2021. Available from: https://www.hqip.org.uk/resource/lung-cancer-ncla-apr23/ . [Access Date: 25 February 2024]. 2023.
25. Cancer Research UK. Lung cancer risk. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/risk-factors#ref-19. [Access Date: 25 February 2024].
26. Cancer Research UK. Lung cancer statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero . [Access Date: 25 February 2024].
27. Cancer Research UK. Cancer mortality for common cancers. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/common-cancers-compared#heading-Zero. [Access Date: 25 February 2024].
28. Deaths registered in England and Wales – 21st century mortality [Access Date: 25 February 2024] [Internet]. 2023. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset.
29. Cancer Research UK. Lung cancer mortality statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/mortality#ref-4. [Access Date: 25 February 2024].

30. NHS Digital. Cancer Survival in England, cancers diagnosed 2016 to 2020, followed up to 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-survival-in-england/cancers-diagnosed-2016-to-2020-followed-up-to-2021 [Access Date: 25 February 2024]. 2023.
31. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26(21):3552-9.
32. Kelsey CR, Marks LB, Hollis D, Hubbs JL, Ready NE, D'Amico TA, et al. Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. Cancer. 2009;115(22):5218-27.
33. National Institute for Health and Care Excellence (NICE). NICE guideline [NG122]. Lung cancer: diagnosis and management. Last updated: 26 July 2023. 2023.
34. National Institute for Health and Care Excellence (NICE). Quality standard [QS17] - Lung cancer in adults. 2019.
35. National Lung Cancer Audit (NCLA). NCLA Lung Cancer Clinical Outcomes Publication (for the 2018 audit period). 2021.
36. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2017;28:iv1-iv21.
37. National Lung Cancer Audit (NCLA). NLCA Annual audit report per the audit period 2019 using Rapid Cancer Registration Data. Available from: https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2022. [Access Date: 05 March 2024]. 2022.
38. National Institute for Health and Care Excellence (NICE). TA876 Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta876 . 2023.
39. Osarogiagbon RU, Lin CC, Smeltzer MP, Jemal A. Prevalence, Prognostic Implications, and Survival Modulators of Incompletely Resected Non-Small Cell Lung Cancer in the U.S. National Cancer Data Base. J Thorac Oncol. 2016;11(1):e5-16.
40. Arriagada R, Auperin A, Burdett S, Higgins JP, Johnson DH, Le Chevalier T, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet. 2010;375(9722):1267-77.
41. Burdett S, Pignon JP, Tierney J, Tribodet H, Stewart L, Le Pechoux C, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. Cochrane Database Syst Rev. 2015(3):Cd011430.
42. Artal Cortés Á, Calera Urquizu L, Hernando Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. Transl Lung Cancer Res. 2015;4(2):191-7.
43. Strauss GM, Herndon JE, 2nd, Maddaus MA, Johnstone DW, Johnson EA, Harpole DH, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol. 2008;26(31):5043-51.
44. Douillard JY, Tribodet H, Aubert D, Shepherd FA, Rosell R, Ding K, et al. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer:

subgroup analysis of the Lung Adjuvant Cisplatin Evaluation. J Thorac Oncol. 2010;5(2):220-8.
45. MSD. Data on File. Early-stage non-small cell lung cancer (NSCLC) Clinical Advisory Board meeting. July 2022.
46. MSD. Data on File. Early-stage non-small cell lung cancer (NSCLC) Clinical Advisory Board meeting. December 2023.
47. MSD. Data on File. Clinical Engagement.
48. Remon J, Soria JC, Peters S. Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy. Ann Oncol. 2021;32(12):1637-42.
49. Chouaid C, Danson S, Andreas S, Siakpere O, Benjamin L, Ehness R, et al. Adjuvant treatment patterns and outcomes in patients with stage IB-IIIA non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. Lung Cancer. 2018;124:310-6.
50. Choi PJ, Jeong SS, Yoon SS. Prognosis of recurrence after complete resection in early-stage non-small cell lung cancer. Korean J Thorac Cardiovasc Surg. 2013;46(6):449-56.
51. Williams BA, Sugimura H, Endo C, Nichols FC, Cassivi SD, Allen MS, et al. Predicting postrecurrence survival among completely resected nonsmall-cell lung cancer patients. Ann Thorac Surg. 2006;81(3):1021-7.
52. Kenny PM, King MT, Viney RC, Boyer MJ, Pollicino CA, McLean JM, et al. Quality of life and survival in the 2 years after surgery for non small-cell lung cancer. J Clin Oncol. 2008;26(2):233-41.
53. Simard S, Savard J, Ivers H. Fear of cancer recurrence: specific profiles and nature of intrusive thoughts. Journal of Cancer Survivorship. 2010;4(4):361-71.
54. Liu M, Liu L, Zhang S, Li T, Ma F, Liu Y. Fear of cancer recurrence and hope level in patients receiving surgery for non-small cell lung cancer: a study on the mediating role of social support. Supportive Care in Cancer. 2022;30(11):9453-60.
55. Hinz A, Mehnert A, Ernst J, Herschbach P, Schulte T. Fear of progression in patients 6 months after cancer rehabilitation—a validation study of the fear of progression questionnaire FoP-Q-12. Supportive Care in Cancer. 2015;23(6):1579-87.
56. Ostroff JS, Krebs P, Coups EJ, Burkhalter JE, Feinstein MB, Steingart RM, et al. Health-related quality of life among early-stage, non-small cell, lung cancer survivors. Lung Cancer. 2011;71(1):103-8.
57. Poghosyan H, Sheldon LK, Leveille SG, Cooley ME. Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: A systematic review. Lung Cancer. 2013;81(1):11-26.
58. Sarna L, Evangelista L, Tashkin D, Padilla G, Holmes C, Brecht ML, et al. Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. Chest. 2004;125(2):439-45.
59. Andreas S, Chouaid C, Danson S, Siakpere O, Benjamin L, Ehness R, et al. Economic burden of resected (stage IB-IIIA) non-small cell lung cancer in France, Germany and the United Kingdom: A retrospective observational study (LuCaBIS). Lung Cancer. 2018;124:298-309.
60. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Dómine M, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non–Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. Journal of Clinical Oncology. 2023;41(11):1992-8.

61. Novello S, Kowalski DM, Luft A, Gümüş M, Vicente D, Mazières J, et al. Pembrolizumab Plus Chemotherapy in Squamous Non–Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. Journal of Clinical Oncology. 2023;41(11):1999-2006.
62. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol. 2021;39(21):2339-49.
63. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol. 2022;23(10):1274-86.
64. Oselin K, Shim BY, Okada M, Bryl M, Bonanno L, Demirag G, et al. Pembrolizumab vs placebo for early-stage non–small-cell lung cancer after resection and adjuvant therapy: Subgroup analysis of patients who received adjuvant chemotherapy in the phase 3 PEARLS/KEYNOTE-091 study. Journal of Clinical Oncology. 2023;41(16_suppl):8520-.
65. MSD. Data on File. KEYNOTE-091 IA3 Clinical Study Report
66. MSD. Data on File. KEYNOTE-091 IA3 Statistical Report.
67. MSD. Data on File. KEYNOTE-091 Clinical Study Protocol.
68. Higgins JPT SJ, Page MJ, Elbers RG, Sterne JAC.,. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.
69. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.
70. Mauguen A, Pignon JP, Burdett S, Domerg C, Fisher D, Paulus R, et al. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: a re-analysis of meta-analyses of individual patients' data. Lancet Oncol. 2013;14(7):619-26.
71. West H, Hu X, Zhang S, Song Y, Chirovsky D, Gao C, et al. Evaluation of disease-free survival as a predictor of overall survival and assessment of real-world burden of disease recurrence in resected early-stage non-small cell lung cancer. J Manag Care Spec Pharm. 2023;29(7):749-57.
72. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol. 2019;37(28):2518-27.
73. National Institute for Health and Care Excellence (NICE). TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta181. 2009.
74. Labbé C, Leung Y, Silva Lemes JG, Stewart E, Brown C, Cosio AP, et al. Real-World EQ5D Health Utility Scores for Patients With Metastatic Lung Cancer by Molecular Alteration and Response to Therapy. Clin Lung Cancer. 2017;18(4):388-95.e4.
75. Yang SC, Lai WW, Chang HY, Su WC, Chen HH, Wang JD. Estimation of loss of quality-adjusted life expectancy (QALE) for patients with operable versus

inoperable lung cancer: adjusting quality-of-life and lead-time bias for utility of surgery. Lung Cancer. 2014;86(1):96-101.
76. Chouaid C, Agulnik J, Goker E, Herder GJ, Lester JF, Vansteenkiste J, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. J Thorac Oncol. 2013;8(8):997-1003.
77. van den Hout WB, Kramer GW, Noordijk EM, Leer JW. Cost-utility analysis of short- versus long-course palliative radiotherapy in patients with non-small-cell lung cancer. J Natl Cancer Inst. 2006;98(24):1786-94.
78. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. Last updated: 31 October 2023. Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation. [Access Date: 29 February 2024].
79. National Institute for Health and Care Excellence (NICE). TA837 Pembrolizumab for adjuvant treatment of resected stage 2B or 2C melanoma. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta837/documents/committee-papers. [Access Date: 29 February 2024]. 2022.
80. National Institute for Health and Care Excellence (NICE). TA851 Pembrolizumab for neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta851/documents/committee-papers. [Access Date: 29 February 2024]. 2022.
81. National Institute for Health and Care Excellence (NICE). TA766 Pembrolizumab for adjuvant treatment of completely resected stage 3 melanoma. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta766/documents/committee-papers. [Access Date: 29 February 2024]. 2022.
82. National Institute for Health and Care Excellence (NICE). TA830 Pembrolizumab for adjuvant treatment of renal cell carcinoma. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta830/documents/committee-papers. [Access Date: 29 February 2024]. 2022.
83. Williams C, Lewsey JD, Briggs AH, Mackay DF. Cost-effectiveness Analysis in R Using a Multi-state Modeling Survival Analysis Framework: A Tutorial. Med Decis Making. 2017;37(4):340-52.
84. Williams C, Lewsey JD, Mackay DF, Briggs AH. Estimation of Survival Probabilities for Use in Cost-effectiveness Analyses: A Comparison of a Multi-state Modeling Survival Analysis Approach with Partitioned Survival and Markov Decision-Analytic Modeling. Med Decis Making. 2017;37(4):427-39.
85. Woods B SE, Palmer S, Latimer N, Soares M.,. NICE DSU Technical Support Document 19. Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. 2017. Available from http://www.nicedsu.org.uk. 2017.
86. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26(11):2389-430.
87. Hinchliffe SR, Lambert PC. Flexible parametric modelling of cause-specific hazards to estimate cumulative incidence functions. BMC Med Res Methodol. 2013;13:13.
88. Latimer N. NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS -

EXTRAPOLATION WITH PATIENT-LEVEL DATA. Last Updated: March 2013. Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD14-Survival-analysis.updated-March-2013.v2.pdf. [Access Date: 29 February 2024]. 2013.
89. National Institute for Health and Care Excellence (NICE). TA761 Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta761/evidence/appraisal-consultation-committee-papers-pdf-10947742237. [Access Date: 29 February 2024]. 2022.
90. National Institute for Health and Care Excellence (NICE). TA939 Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer. Available from: https://www.nice.org.uk/guidance/ta939. [Access Date: 29 February 2024]. 2023.
91. Lipson EJ, Sharfman WH, Drake CG, Wollner I, Taube JM, Anders RA, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin Cancer Res. 2013;19(2):462-8.
92. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. New England Journal of Medicine. 2020;382(9):810-21.
93. Luke JJ, Ascierto PA, Khattak MA, de la Cruz Merino L, Del Vecchio M, Rutkowski P, et al. Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the phase 3 KEYNOTE-716 study. Journal of Clinical Oncology. 2023;41(17_suppl):LBA9505-LBA.
94. Robert C, Carlino MS, McNeil C, Ribas A, Grob JJ, Schachter J, et al. Seven-Year Follow-Up of the Phase III KEYNOTE-006 Study: Pembrolizumab Versus Ipilimumab in Advanced Melanoma. J Clin Oncol. 2023;41(24):3998-4003.
95. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018-28.
96. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol. 2019;30(4):582-8.
97. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33.
98. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol. 2019;37(7):537-46.
99. National Institute for Health and Care Excellence (NICE). TA823 Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer. Commitee Papers. Available from: https://www.nice.org.uk/guidance/ta823/documents/committee-papers. [Access Date: 29 February 2024]. 2022.
100. National Institutes of Health (NIH). SEER data 2007-2017 - Medicare claims data: 2007-2019. Available from: https://healthcaredelivery.cancer.gov/seermedicare/. .

101. National Institutes of Health (NIH). SEER-Medicare: Brief Description of the SEER-Medicare Database. Available from: https://healthcaredelivery.cancer.gov/seermedicare/overview/. .
102. Nakamichi S, Horinouchi H, Asao T, Goto Y, Kanda S, Fujiwara Y, et al. Comparison of Radiotherapy and Chemoradiotherapy for Locoregional Recurrence of Non-small-cell Lung Cancer Developing After Surgery. Clin Lung Cancer. 2017;18(6):e441-e8.
103. Kruser TJ, McCabe BP, Mehta MP, Khuntia D, Campbell TC, Geye HM, et al. Reirradiation for locoregionally recurrent lung cancer: outcomes in small cell and non-small cell lung carcinoma. Am J Clin Oncol. 2014;37(1):70-6.
104. Moore S, Leung B, Wu J, Ho C. Survival Outcomes of Salvage Therapy for Local and Regionally Recurrent NSCLC. JTO Clinical and Research Reports. 2020;1(4):100083.
105. National Institute for Health and Care Excellence (NICE). TA798 Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation. Available from: https://www.nice.org.uk/guidance/ta798. 2022.
106. NHS England. National Cancer Drugs Fund list. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1.294.pdf. [Access Date: 28 February 2024].
107. MSD. Data on File. Network meta-analysis of interventions for the first-line treatment of metastatic NSCLC patients. Technical Report. v2. .
108. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med. 2020;382(1):41-50.
109. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(2):113-25.
110. Polanco D, Pinilla L, Gracia-Lavedan E, Mas A, Bertran S, Fierro G, et al. Prognostic value of symptoms at lung cancer diagnosis: a three-year observational study. J Thorac Dis. 2021;13(3):1485-94.
111. Sofia H, Chirag H, Dana L, Rahul M. The Burden of Asymptomatic Lung Cancer. European Respiratory Journal. 2019;54(suppl 63):PA3038.
112. Park SE, Lee SH, Ahn JS, Ahn MJ, Park K, Sun JM. Increased Response Rates to Salvage Chemotherapy Administered after PD-1/PD-L1 Inhibitors in Patients with Non-Small Cell Lung Cancer. J Thorac Oncol. 2018;13(1):106-11.
113. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(17):1627-39.
114. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255-65.
115. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-50.

116. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(2):123-35.
117. Schvartsman G, Peng SA, Bis G, Lee JJ, Benveniste MFK, Zhang J, et al. Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer. Lung Cancer. 2017;112:90-5.
118. Grigg C, Reuland BD, Sacher AG, Yeh R, Rizvi NA, Shu CA. Clinical outcomes of patients with non-small cell lung cancer (NSCLC) receiving chemotherapy after immune checkpoint blockade. Journal of Clinical Oncology. 2017;35(15_suppl):9082-.
119. Leger PD, Rothschild S, Castellanos E, Pillai RN, York SJ, Horn L. Response to salvage chemotherapy following exposure to immune checkpoint inhibitors in patients with non-small cell lung cancer. Journal of Clinical Oncology. 2017;35(15_suppl):9084-.
120. Diker O, Olgun P. Salvage chemotherapy in patients with nonsmall cell lung cancer after prior immunotherapy: a retrospective, real-life experience study. Anticancer Drugs. 2022;33(8):752-7.
121. Heraudet L, Delon T, Veillon R, Vergnenègre C, Lepetit H, Daste A, et al. Effect of prior immunotherapy on the efficacy of chemotherapy in advanced non-small cell lung cancer: A retrospective study. Thorac Cancer. 2022;13(9):1391-400.
122. Saleh K, Khalifeh-Saleh N, Kourie HR, Nasr F, Chahine G. Do immune checkpoint inhibitors increase sensitivity to salvage chemotherapy? Immunotherapy. 2018;10(3):163-5.
123. EuroQoL. EuroQol Instruments - EQ-5D-3L, EQ-5D-5L, EQ-5D-Y. Available from: https://euroqol.org/. [Access Date: 25 February 2024].
124. National Institute for Health and Care Excellence (NICE). TA683 (CDF review of TA557) Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta683. [Access Date: 05 March 2024]. 2021.
125. National Institute for Health and Care Excellence (NICE). TA770 (CDF review of TA600) Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta770. [Access Date: 05 March 2024]. 2022.
126. Leiter A, Kong CY, Gould MK, Kale MS, Veluswamy RR, Smith CB, et al. The benefits and harms of adjuvant chemotherapy for non-small cell lung cancer in patients with major comorbidities: A simulation study. PLoS One. 2022;17(11):e0263911.
127. Scottish Medicines Consortium (SMC). SMC2383 - Osimertinib 40mg and 80mg film-coated tablets (Tagrisso®). Detailed Advice Document. Available from: https://www.scottishmedicines.org.uk/media/6422/osimertinib-tagrisso-final-october-2021-for-website.pdf. [Access Date: 29 February 2024].
128. Scottish Medicines Consortium (SMC). SMC2492 - Atezolizumab 840mg and 1,200mg concentrate for solution for infusion (Tecentriq®). Detailed Advice Document. Available from: https://www.scottishmedicines.org.uk/media/7043/atezolizumab-tecentriq-final-july-2022-amended-130722-for-website.pdf. [Access Date: 27 October 2023].
129. Yip C-y, Greystoke A, Abogunrin S, Belleli R, Di Maio D, Rouse P, et al. Cost-effectiveness analysis of adjuvant atezolizumab in stage II-IIIA non-small cell lung

cancer expressing ≥50% PD-L1: A United Kingdom health care perspective. Lung Cancer. 2023;179:107171.
130. Jang RW, Isogai PK, Mittmann N, Bradbury PA, Shepherd FA, Feld R, et al. Derivation of Utility Values from European Organization for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire Values in Lung Cancer. Journal of Thoracic Oncology. 2010;5(12):1953-7.
131. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18.
132. Apple J, DerSarkissian M, Shah A, Chang R, Chen Y, He X, et al. Economic burden of early-stage non-small-cell lung cancer: an assessment of healthcare resource utilization and medical costs. J Comp Eff Res. 2023:e230107.
133. Buck PO, Saverno KR, Miller PJ, Arondekar B, Walker MS. Treatment patterns and health resource utilization among patients diagnosed with early stage resected non-small cell lung cancer at US community oncology practices. Clin Lung Cancer. 2015;16(6):486-95.
134. Cai B, Fulcher N, Boyd M, Spira A. Clinical outcomes and resource utilization after surgical resection with curative intent among patients with non-small cell lung cancer treated with adjuvant therapies in a community oncology setting: a real-world retrospective observational study. Thorac Cancer. 2021;12(14):2055-64.
135. Cai B, Fulcher N, Boyd M, Spira A. CP01.05 relapse rate and associated healthcare resource utilization in stage IIA-IIIB adjuvant NSCLC patients treated in a US oncology community network. J Thorac Oncol. 2021;16(1):S13-S4.
136. Sharma R, Ogale S, Smith NJ, Lee JS. Estimating recurrences prevented and costs avoided with atezolizumab in early non-small cell lung cancer in the United States. Cancer Med. 2023;12(6):7450-8.
137. Wang Z, Askamit I, Tuscher L, Bergstrom K. Rates of guideline adherence among US community oncologists treating NSCLC. Am J Manag Care. 2013;19(3):185-92.
138. West H, Hu X, Chirovsky D, Walker MS, Wang Y, Kaushiva A, et al. Clinical and economic impact of recurrence in early-stage non-small-cell lung cancer following complete resection. Future Oncol. 2023;19(20):1415-27.
139. Mahar AL, Coburn NG, Johnson AP. A population-based study of the resource utilization and costs of managing resectable non-small cell lung cancer. Lung Cancer. 2014;86(2):281-7.
140. Singnurkar A, Swaminath A, Metser U, Langer DL, Darling GE, Pond GR. The impact of synchronous malignancies on survival in patients with early stage curable non-small-cell lung cancer. Cancer Treat Res Commun. 2020;25:100246.
141. Buja A, Rivera M, De Polo A, Brino ED, Marchetti M, Scioni M, et al. Estimated direct costs of non-small cell lung cancer by stage at diagnosis and disease management phase: a whole-disease model. Thorac Cancer. 2021;12(1):13-20.
142. Cortinovis DL, Perrone V, Giacomini E, Sangiorgi D, Andretta M, Bartolini F, et al. Epidemiology, Patients' Journey and Healthcare Costs in Early-Stage Non-Small-Cell Lung Carcinoma: A Real-World Evidence Analysis in Italy. Pharmaceuticals (Basel). 2023;16(3).
143. Byun JY, Lee JE, Shim YB, Kim J, Lee SY, Shin BR, et al. Economic Burden of Recurrence in Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer: A Retrospective Study Using Nationwide Claims Data of South Korea. Adv Ther. 2023;40(2):550-67.

144. National Institute for Health and Care Excellence (NICE). TA904 Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta904. [Access Date: 05 March 2024]. 2023.
145. National Institute for Health and Care Excellence (NICE). TA654 Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer | Guidance | NICE. Available from: https://www.nice.org.uk/guidance/TA654 . 2020.
146. NHS England. NHS Reference Costs. 2021/22 National Cost Collection Data Publication. Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/. [Access Date: 29 February 2024].
147. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care programme (2022 – 2027). Available from: https://www.pssru.ac.uk/unitcostsreport/. [Access Date: 29 February 2024].
148. National Institute for Health and Care Excellence (NICE). NICE guideline [NG122]. Lung cancer: diagnosis and management. Evidence reviews for the clinical and costeffectiveness of routine MRI or CT of the brain in the management of people with lung cancer prior to therapy with curative intent . Evidence reviews B (2019). Last updated: 26 July 2023. Available from: https://www.nice.org.uk/guidance/ng122/evidence/b-clinical-and-costeffectiveness-of-routine-mri-or-ct-of-the-brain-in-the-management-of-people-with-lung-cancer-prior-to-therapy-with-curative-intent-pdf-6722112207. 2023.
149. Emc. TAGRISSO 40 mg film-coated tablets. Summary of Products Characteristics. Available from: https://www.medicines.org.uk/emc/product/1985/smpc#gref. [Access Date: 29 February 2024].
150. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2018;379(21):2040-51.
151. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2018;378(22):2078-92.
152. 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.
153. Emc. Docetaxel 20 mg/ml concentrate for solution for infusion. Summary of Product Characteristics. Available from: https://www.medicines.org.uk/emc/product/7206/smpc. [Access Date: 29 February 2024].
154. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol. 2000;18(12):2354-62.
155. Flatiron. Flatiron Health database. Claims-Linked EHR Data. https://flatiron.com/real-world-evidence/claims-linked-ehr-data. Data cutoff: 31 May 2023. Data on file. 2023.
156. Georghiou T and Bardsley M. Exploring the cost of care at the end of life. Research report [Internet]. Nuffield Trust. Available from:

https://www.nuffieldtrust.org.uk/research/exploring-the-cost-of-care-at-the-end-of-life. . 2014.
157. National Institute for Health and Care Excellence (NICE). TA801 Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta801. [Access Date: 05 March 2024]. 2022.

B.5. Appendices

All appendices are provided in separate documents. Please note that Appendix L (Checklist of confidential information) is provided as a standalone checklist of confidential information document.

- Appendix C: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Subgroup analysis
- Appendix F: Adverse reactions
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality-of-life studies
- Appendix I: Cost and healthcare resource identification, measurement and valuation
- Appendix J: Clinical outcomes and disaggregated results from the model
- Appendix K: Price details of treatments included in the submission
- Appendix L: Checklist of confidential information
- Appendix M: KEYNOTE-091 additional study methodology information and result
- Appendix N: Final Model Selection
- Appendix O: Baseline characteristics of SEER-Medicare
- Appendix P: Flatiron database methodology

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Summary of Information for Patients (SIP)

March 2024

File name	Version	Contains confidential information	Date
NICE ID3907 Pembrolizumab adjuvant NSCLC - SIP	1.0	No	12 March 2024

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

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

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

Pembrolizumab (KEYTRUDA®)

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

Pembrolizumab has been approved as an adjuvant treatment of adults with non-small cell lung cancer that is at its early stages (stage IB with tumours with size ≥ 4 cm to IIIA under 7th edition of AJCC staging criteria) after the tumour has been resected via surgery followed by adjuvant treatment with chemotherapy. An adjuvant treatment is used after the main treatment, such as surgery, to lessen the chance of the cancer coming back. Even if surgery succeeds at removing all visible cancer, microscopic bits of cancer sometimes remain and are undetectable with current methods. An adjuvant immunotherapy like pembrolizumab aims to eliminate any remaining cancer cells by stimulating the body's immune system. The exact indication in which pembrolizumab has been approved is reported in section 1c. The submission that is being appraised by NICE focuses on a subgroup of the indication above, which is patients whose tumours have programmed death-ligand 1 (PD-L1) biomarker expression on less than 50% of their tumour cells (PD-L1 TPS <50%). More details of this biomarker are included in section 2b and 3a.

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.

Pembrolizumab has received a positive opinion by the Committee assessing the efficacy and safety of the medicines (Committee for Medicinal Products for Human Use - CHMP) in the European Union (EU) on 14 September 2023, followed by the European Commission Decision on 12 October 2023, for the following indication: "*KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy*". (1)
The application for obtaining Marketing Authorisation for the same indication in the United Kingdom was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA), the Agency responsible for medicine approval in the UK, on 19 September 2023. Approval for the same indication was obtained on 18 December 2023. (2)

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:

The table below describes MSD's involvement with the patient groups that are listed as stakeholders for this appraisal.

Stakeholder	Financial transaction in 2023/2024	Have met with MSD	Relationship
Asthma and Lung UK	N	Y	We have met to share annual plans/projects, discuss policy and landscape, and share learnings.
Black Health Agency for Equality	N	N	
Cancer Black Care	N	N	
Cancer Equality	N	N	
Cancer Research UK	N	Y	We have met to share annual plans/projects, discuss policy and landscape, and share learnings.
Helen Rollason Cancer Charity	N	N	
Independent Cancer Patients Voice	N	N	
Less Survival Cancers Task Force	£20,000 (2023) £20,000 (2024)	Y	MSD is a corporate member for the 2024 calendar year and was also a member for the 2023 calendar year. We have met to share annual plans/projects, discuss policy and landscape, and share learnings.
Macmillan Cancer Support	N	Y	We have met to share annual plans/projects, discuss policy and landscape, and share learnings
Maggie's Centres	N	Y	MSD's clinical trials team has met to provide insight into the clinical trial process from concept to data readout.
Marie Curie	N	N	
Roy Castle Lung Cancer Foundation	£4060 (2023)	Y	MSD had an agreement with RCLCF for their input, steer and expertise in the MSD-sponsored Lung Cancer Awareness Month Parliamentary event in 2023. We have

			met to share annual plans/projects, discuss policy and landscape, and share learnings.
South Asian Health Foundation	N	N	
Specialised Healthcare Alliance	N	N	
Taskforce of Lung Health	N	Y	We have met to share annual plans/projects, discuss policy and landscape, and share learnings.
Tenovus Cancer Care	£7560 (2023)	Y	MSD sponsored a roundtable event for thought leaders to discuss upper GI and oesophageal cancer and issues in Wales. We have met to share annual plans/projects, discuss policy and landscape, and share learnings. We have also participated in meetings where both parties were supporting a lung health check project.
UK Lung Cancer Coalition	£27,500(2023), £20,000 (2024)	Y	Sponsorship of the UKLCC National Conference 2023. Corporate membership for the 2023 and 2024 calendar year. MSD supported the UKLCC to produce a report assessing the state of current lung cancer pathways to support the implementation of the Scottish National Optimal Lung Cancer Pathway. We have met to share annual plans/projects, discuss policy and landscape, and share learnings.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

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 can start in any part of the lungs or airways. It develops when there is uncontrolled growth of abnormal cells inside one or both lungs. These cells grow to form tumours. [3]
Lung cancers can be divided into two main groups: small cell lung cancer (SCLC), mainly starting near a central bronchus, and non-small cell lung cancer (NSCLC), which usually develops in the peripheral tissues of the lung. [3] NSCLC is also the most frequent (approximately 88% of lung cancer cases). [4] The indication being appraised only involves NSCLC.
Unlike the tumours diagnosed at stage I, tumours at stages II-III may have larger size and spread to the lymph nodes or to other areas on the same side of the body. [5]
Lung cancer is the second most common cancer type and the main cause of cancer death worldwide [6]. In the UK, it is the third most common cancer [7]; around 35,000 people were diagnosed with lung cancer in England in 2021. [8]Lung cancer constitutes the most common cause of cancer death in the UK (34,771 on average every year, corresponding to 21% of all cancer deaths). [9] Overall, only 44.9% of people diagnosed with lung cancer in England have survived their disease for one year or more. The percentage increases when patients are diagnosed at early

stage (between 52.6% and 88.1% depending on disease stage). [10] However, the risk of recurrences at early stage is still high. [11]
Lung cancer may remain asymptomatic and undiagnosed until the disease is well advanced unless patients undergo chest examination for other reasons. [12]
The most common symptoms associated with NSCLC are frequent cough, haemoptysis (coughing up sputum with blood in it), chest and shoulder pain, getting out of breath while carrying out usual activities (dyspnoea), hoarse voice, weight loss, feeling tired. [13] [12] Therefore, it has a tremendous impact on the quality of life of patients.

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?

People with suspected lung cancer undergo different tests such as chest X-ray and contrast-enhanced chest CT or scan that will create detailed pictures of the inside of the body to confirm the diagnosis and determine the stage the disease. Biopsy or further imaging may be additionally needed for staging and to detect specific markers, e.g., gene mutations or proteins that can guide treatment strategy.[14] More specifically, an additional test can be performed to verify whether the tumour cells and immune cells of the patients express a specific biomarker (PD-L1), and patients' suitability to receive immunotherapies such as pembrolizumab or atezolizumab. Therefore, this additional test is required if pembrolizumab is recommended. Since this test has a quick turnaround time, it is expected this test to be implemented at earlier stages with no additional administrative burden.

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:
    - 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.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

In early-stage NSCLC (stages I-IIIA) main treatments of choice are delivered with the purpose of eliminating the cancer. If the tumour can be removed and, based on the health status of lungs and heart and risks associated with the surgical procedure, surgery is the preferred treatment option. [15] Patients who decline surgery or in whom surgery is contraindicated, can receive radiotherapy. [16]

Chemotherapy after surgery has become an additional option as an adjuvant treatment to further reduce the risk of recurrence. Chemotherapy combinations that include cisplatin are currently offered in England to people who are fit enough and whose tumour has spread to the lymph nodes; in patients who are fit enough whose tumour has not spread to lymph nodes, adjuvant chemotherapy can also be considered. [16]Patients' suitability to the adjuvant treatment depends on many factors e.g., pre-existing comorbidity, time from surgery and recovery after surgery. There are no additional adjuvant treatments in the established practice available for people that undergo surgical resection.

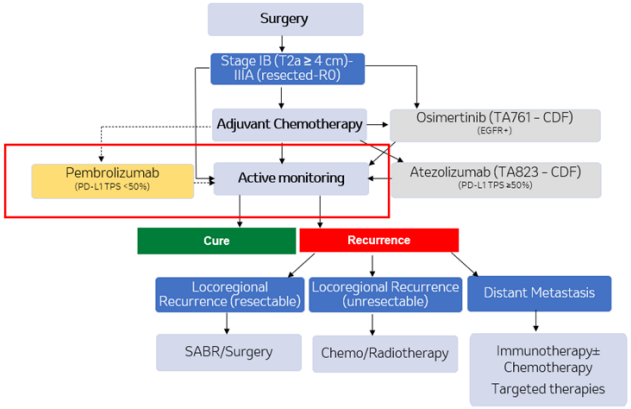
Two drugs are currently recommended for these patients within the Cancer Drugs Fund, which is a time-limited source of funding: atezolizumab for patients whose tumours have the PD-L1 biomarker expression on 50% or more of their tumour cells [17], and osimertinib for patients whose tumours carry a specific mutation (EGFR). [18]

For any other patients that are not eligible for these temporarily funded treatments, surgery and adjuvant chemotherapy (where suitable) are therefore followed by active monitoring which clinicians describe as CT scans repeated at regular intervals such as every 3-6 months, becoming less frequent after 1 year. [19]

Through this appraisal MSD are aiming to seek a NICE recommendation for pembrolizumab for the subgroup of patients with early-stage NSCLC (stage IB with tumours with size ≥ 4 cm to IIIA based on 7th edition of AJCC staging criteria, corresponding to IIA through IIIB [N2] based on 8th edition) following complete surgical resection and adjuvant chemotherapy, whose tumours have PD-L1 biomarker expression on less than 50% of their tumour cells (PD-L1 TPS <50%). These are the patients with higher unmet medical need as there are no adjuvant therapy available for them, either routinely used or available through temporary source of funding.

The diagram below shows the proposed positioning of pembrolizumab, subject to this appraisal. The boxes in grey refer to the drugs currently available through the Cancer Drugs Fund (CDF).

Table 1 Proposed positioning of pembrolizumab relative to the current pathway



Abbreviations: CDF: Cancer Drugs Fund; EGFR: Epidermal Growth Factor Receptor; NSCLC: Non-small cell Lung cancer; PD-L1: programmed death-ligand 1; TPS: tumour proportion score.

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.

Patients with lung cancer are faced with many challenges, including the difficulties associated with post-surgery symptoms and the mental and emotional impacts associated with the diagnosis of a potentially fatal illness.

The most common symptoms among lung cancer patients after surgical treatment are pain, fatigue, dyspnoea (shortness of breath) and coughing. A review of available evidence on symptoms after surgery found that scores associated with the severity of the symptoms remained significantly worse compared to before surgery after 3–4 months. This may vary depending on type of surgery and age. Dyspnoea was found to be common even 2–3-years after surgery. [20]
This symptom may have a tremendous impact on everyday life. Even among cancer survivors, some patients reported spending most of the day in bed in the previous 12 months because of respiratory symptoms. Other survivors described themselves as so breathless they could not leave the house. [21]

Some patients receive chemotherapy after surgery. This can result in further issue due to the side effects of chemotherapy. Each person experiences side effects from chemotherapy differently, and different chemotherapy drugs cause different side effects. [22]Many people feel fine for the first few hours following chemotherapy. Usually, some reaction occurs about four to six hours later. However, some people do not react until 12 or even 24 to 48 hours after treatment. Some of the most common side effects are summarised below [23]:

- feeling sick
- loss of appetite
- losing weight
- feeling very tired
- increased risk of getting an infection
- bleeding and bruising easily
- diarrhoea or constipation
- hair loss

In addition to the physical symptoms, many patients live with the fear that the cancer will return or progress in the same organ or in another part of the body (fear of cancer recurrence or FCR) which persists a long time after the termination of cancer treatments. [24]
Patients may engage in unhelpful negative behaviours to cope with this fear, such as excessive medical testing or avoidance, that lead to disruptions in daily life and a limited capacity to plan for the future. This can also result in significant psychological distress and reduced quality of life (QOL).[25]

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

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.

An important role of the immune system is the ability to be able to tell the difference between healthy and unhealthy cells. The level of activity of immune cells, such as T cells, is crucial to maintaining a balanced immune response.

Under normal conditions, a protein called programmed death-ligand 1 (PD-L1) which naturally occurs on cells, plays an important role in maintaining this balanced immune response. PD-L1 binds to its PD-1 receptor on immune T cells, which lessens the ability of immune T cells to attack. This ensures that normal cells are protected from excessive damage. However, PD-L1 is produced in larger amounts on cancerous cells than normal cells. As a result, when binding to PD-1 on immune T cells, this interaction tricks the immune system thereby protecting the tumour from being attacked by the body's immune system.

PD-1 inhibitors, such as pembrolizumab, act to block the interaction between PD-1 and PD-L1 and by doing so, boost the immune response which helps the person's own immune cells to attack the cancer cells.

The summary of product characteristics (SmPC) and the patient information leaflet (PIL) for pembrolizumab can be found by following this link:

KEYTRUDA

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.**
No, pembrolizumab is intended to be administered as a single drug for this indication.

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?
Pembrolizumab comes in a 25mg/mL concentrate solution for infusion. One 4mL vial of concentrate contains 100 mg of pembrolizumab. The recommended dose of KEYTRUDA in adults is either 200 mg every three weeks (Q3W) or 400 mg every six weeks (Q6W) administered as an infusion into the vein (intravenous infusion) over 30 minutes. This can be a quicker infusion compared to standard chemotherapy. Administration every six weeks can be particularly convenient for those patients who do not have access to clinics in the proximity of the area where they live and need to travel long distances to receive effective therapies.

In line with its licence, pembrolizumab may be given for up to Q3W 18 cycles (approximately one year) as long as it is working (i.e. as long as the cancer does not progress) and side effects are tolerable. [2]

Scans are conducted regularly to keep track of response to treatment. Patients need to be monitored while on treatment for symptoms or side effects, and blood tests may be conducted to check for side effects.

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.

A search on clinicaltrials.gov for recruiting, enrolling by invitation, active but not recruiting, or completed studies on pembrolizumab returned 1,735 records (search conducted on 20th February 2024). 68 of these studies were Phase 3 trials conducted in non-small cell lung cancer, and 6 were studies in stage I-III non-small cell lung cancer and are listed below. Further details of these studies can be found by searching for the study name on clinicaltrials.gov.

Study Title	NCT Number	Status	Phase	Condition	Interventions	N of patients	Estimated Completion Date
Efficacy and Safety of Pembrolizumab (MK-3475) With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage II, IIIA, and Resectable IIIB (T3-4N2) Non-small Cell Lung Cancer (MK-3475-671/KEYNOTE-671)	NCT03425643	Active Not Recruiting	3	Non-small Cell Lung Cancer	Pembrolizumab, Cisplatin, either Gemcitabine or Pemetrexed	797	10/07/2023
Study of Pembrolizumab (MK-3475) vs Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-3475-091/KEYNOTE-091)	NCT02504372	Active Not Recruiting	3	Non-small Cell Lung Cancer	Pembrolizumab	1177	24/01/2023

A Study of V940 Plus Pembrolizumab (MK-3475) Versus Placebo Plus Pembrolizumab in Participants With Non-small Cell Lung Cancer (V940-002)	NCT06077760	Recruiting	3	Non-small Cell Lung Cancer	Pembrolizumab, V940	868	25/06/2030
Study of Pembrolizumab With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib in Stage III Non-Small Cell Lung Cancer (NSCLC) (MK-7339-012/KEYLYNK-012)	NCT04380636	Active Not Recruiting	3	Non-small Cell Lung Cancer	Pembrolizumab+chemoradiation (carboplatin or cisplatin + pemetrexed or paclitaxel + radiotherapy), followed by pembrolizumab+olaparib	870	06/07/2026
Efficacy and Safety Study of Stereotactic Body Radiotherapy (SBRT) With or Without Pembrolizumab (MK-3475) in Adults With Unresected Stage I or II Non-Small Cell Lung Cancer (NSCLC) (MK-3475-867/KEYNOTE-867)	NCT03924869	Active Not Recruiting	3	Non-small Cell Lung Cancer	Stereotactic Body Radiotherapy + Pembrolizumab	436	11/04/2025
Study of Pembrolizumab/Vibostolimab (MK-7684A) in Combination With Concurrent Chemoradiotherapy Followed by Pembrolizumab/Vibostolimab	NCT05298423	Recruiting	3	Non-small Cell Lung Cancer	Pembrolizumab + vibostolimab in combination with concurrent chemoradiotherapy [(cisplatin + pemetrexed OR cisplatin + etoposide OR carboplatin+ paclitaxel) + thoracic radiotherapy]	784	01/09/2028

Versus Concurrent Chemoradiotherapy Followed by Durvalumab in Participants With Stage III Non-small Cell Lung Cancer (MK-7684A-006/KEYVIBE-006)							

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.

The KEYNOTE-091 study was conducted to see how well pembrolizumab worked in patients with early-stage NSCLC after they underwent surgery to remove the tumour followed by adjuvant treatment with chemotherapy (if the patients were suitable for it), in comparison with placebo (treatment with no active substance).

To find this out the following key measures were taken:

Disease free survival – disease-free survival, or DFS, measures how long a person lives without the cancer coming back (recurrence) or until death from the start of the trial. Taking the median, an average, typically measured in months or weeks, DFS can be a useful measure of how long a patient may expect to live without the cancer coming back after starting to take the medicine in the trial. The hazard ratio (HR) measures the average risk of experiencing a recurrence or dying after starting to take the medicine in the trial compared to another medicine or placebo.

Overall survival – overall survival, or OS, measures how long a person lives from the start of the trial until death. Taking the median, an average, typically measured in months or weeks, OS can be a useful measure of how long a patient may expect to live after starting to take the medicine in the trial. The hazard ratio (HR) measures the average risk of dying after starting to take the medicine in the trial compared to another medicine or placebo.

The data below are related to the subgroup within the study population that has received chemotherapy after surgery, whose tumours have PD-L1 biomarker expression on less than 50% of their tumour cells (PD-L1 TPS <50%). This is the subgroup for which MSD are seeking a NICE recommendation.

DFS results - KEYNOTE-091 demonstrated an increased clinical benefit for the patients treated with pembrolizumab compared with placebo. The hazard ratio for DFS was 0.72 [95% CI: 0.58, 0.89] which corresponds to 28% reduction in the risk of the cancer coming back or dying after starting to take pembrolizumab compared with placebo. Please note that in addition to the HR value, a range is also provided in brackets. This range refers to an upper and lower estimate between which you can be 95% certain the true value lies, named 95% confidence interval (CI). On average, pembrolizumab patients lived 17 months more without recurrence compared to patients in the placebo group (median DFS of 51.5 months versus 34.5 months for patients in the pembrolizumab and placebo group, respectively).

OS results – the results suggest an improvement in the risk of dying for patients treated with pembrolizumab compared to patients in the placebo group, with HR of 0.73 [95% CI: 0.55, 0.97]. However, a low number of deaths had occurred before the analysis was conducted to be able to establish the actual benefit of pembrolizumab in reducing the risk of dying. The median in both the pembrolizumab and placebo groups is NR which refers to “Not Reached”. This means that the studies have not yet been running for long enough for us to make a measurement.

More information is provided in the submission document B, section B.2.6.

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.

Quality of life data such as patient reported outcomes (PROs) were collected in the KEYNOTE-091 study by using two types of questionnaire, the EORTC QLQ-C30/EORTC QLQ-LC13, that looks specifically at the quality of life of cancer patients, and the EQ-5D, that looks at a the general health status of a patient. [(26)]

The EQ-5D consists of 2 sections: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system has five questions on mobility, self-care, pain, usual activities, and psychological status with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem). Results from these questions can then be combined and scaled to produce a single score with a maximum score of 1. Scores can vary from 0, which represents death, to 1 which represents the best possible health state. The EORTC uses different questions, however also produces a score that is meant to represent a patient's quality of life. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. From this we can gather three scores (from the EQ-5D questionnaire, the EQ-5D VAS and the EORTC questionnaire) that can assess how a patient feels throughout their treatment.

In the KEYNOTE-091 study these outcomes were collected before the study patients received the treatment (baseline) and at week 48 where a high proportion of patients was expected to have completed the questionnaires. The following data will describe how much on average the quality life of patients has changed since the start of the treatment ("mean change from baseline"). Across all three methods, the change from baseline at week 48 was not considered clinically meaningful in either treatment groups. The change from baseline for EQ-5D VAS and EORTC QLQ-C30 remained stable over time in either treatment groups. No substantial difference in the change from baseline between the two arms was observed.

More information is provided in the submission document B, section B.2.6.5 and Appendix M.

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.

The most frequent side effects (adverse events) are reported below for the KEYNOTE-091 study population.

Please note that the below table include any adverse events experienced whilst patients were on the clinical trial, including but not limited to the side effects caused by pembrolizumab. "N" refers to the number of patients in the trial and "%" refers to the proportion.
The overall proportion of participants with adverse events was similar in the pembrolizumab group compared with the placebo group (95.9% vs 91.0%). The adverse events that were reported in at least 20% of patients in one or both treatment groups were weight increased, pruritus and hypothyroidism (reduced thyroid gland activity).

Table 2 KEYNOTE-091 Most frequent adverse events (Database Cutoff Date: 20 September 2021)

Adverse event	**Pembrolizumab**		**Placebo**	
	N	**(%)**	**N**	**(%)**
Total number of patients	580		581	
Patients with one or more adverse events	556	(95.9)	529	(91.0)
Weight increased	133	(22.9)	168	(28.9)
Pruritus (itching)	125	(21.6)	74	(12.7)
Hypothyroidism (reduced thyroid gland activity)	120	(20.7)	27	(4.6)
Arthralgia (joint pain)	108	(18.6)	75	(12.9)
Diarrhoea	106	(18.3)	83	(14.3)
Fatigue (feeling tired)	96	(16.6)	89	(15.3)
Cough	87	(15.0)	98	(16.9)
Hypertension (high blood pressure)	67	(11.6)	74	(12.7)
Dyspnoea (shortness of breath)	66	(11.4)	72	(12.4)
Hyperthyroidism (overactive thyroid gland activity)	62	(10.7)	17	(2.9)

Most of the adverse events were Grade 1 or 2 (mild to moderate severity).
The grading system for adverse events referred to above is explained in section 4a.

As described in the pembrolizumab Patient Information Leaflet (PIL), doctors can manage side effects such as immune-related side effects and reduce symptoms by prescribing other medicines such as corticosteroids or withholding the next dose of pembrolizumab or stopping the treatment with pembrolizumab. [27]

The side effects reported in KEYNOTE-091 study are consistent with the common side effects listed in the pembrolizumab Summary of Product Characteristics (SmPC). [27]This published document gives doctors and other hospital staff clear guidance on what side effects to expect and what to do if a patient experiences a side effect based on all the trials that have led to the licences in which pembrolizumab can be used.

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
• Pembrolizumab reduces the risk of the cancer coming back. This means that it may stop the cancer from progressing to stages where treatments aiming to cure the disease are not available. • Though long follow-up data are needed, pembrolizumab may improve patients' life expectancy vs active monitoring. • Most of the side effects that patients can potentially experience while on treatment or after are of mild or moderate severity. Overall, the benefit-risk ratio for pembrolizumab in this indication is considered positive. • While this treatment requires infusion every three or six weeks for up to a year, resulting in more frequent visits to hospital compared to active monitoring, pembrolizumab does not negatively affect quality of life. • The infusion time of pembrolizumab is short compared to some of the chemotherapies used in the adjuvant setting, and pembrolizumab can be given every six weeks. This could result in shorter and less frequent visits to a hospital for patients.

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
• Patients are at an increased risk of developing immune-related side effects, some of which may last beyond the patient stopping pembrolizumab. Please note there is clear guidance provided in the SmPC that instructs healthcare providers on how to manage these side effects. • Pembrolizumab, like any other medicine, does not work the same in every patient. Not all patients' cancers will respond to treatment, and it may not prevent the cancer from coming back or result in an extended life expectancy.

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.

Cost-effectiveness relates to how much new health (or quality-adjusted life years, QALYs) the new medicine produces compared to its additional cost (vs. current care), for a typical/average patient and whether the new health is worth the extra cost required to pay for it.

The cost-effectiveness of pembrolizumab is evaluated for the typical/average patient via modelling that uses trial data from KEYNOTE-091 to predict clinical effectiveness (efficacy) and costs over 35.7 years. The model comprises of four-health states: disease free, local-regional recurrence, distant metastases, and death. The challenges of modelling average lifetime outcomes (overall survival, efficacy of downstream treatments and quality-of-life) from trial data arises as there was limited data collected for those patients who experienced local-regional recurrence as their first event. Consequently, the later transitions in the model (local-regional recurrence to distant metastases, distant metastases to death and local-regional recurrence to death) could not be estimated in the model using data from the KEYNOTE-091 trial. Local-regional recurrence to distant metastases and local-regional recurrence to death were instead sourced using external real-world data (SEER-Medicare), while transitions from distant metastases were informed by calculating the exponential rates from OS and PFS from published metastatic trials for first-line. The transitions have some time-limited calibration or adjustment to match the modelled OS to OS from the KEYNOTE-091 trial.

In adjuvant appraisals, the efficacy and costs of downstream treatments or subsequent treatments are an important consideration, and these were captured in the KEYNOTE-091 model. The efficacy for first-line metastatic regimens were informed as already described above and no efficacy was included for second-line distant metastatic treatments. Resource use for first-line and second-line metastatic regimens were informed by MSD's 2022 Advisory Board.

Quality-of-life data (disease free and local-regional recurrence health states and adverse events) were available from the KEYNOTE-091 trial of pembrolizumab. The utility for the distant metastatic state was derived from the progression free and progressed disease utility data from a previous metastatic trial of pembrolizumab (KEYNOTE-189 and KEYNOTE-407). The utilities from KEYNOTE-091 and these pivotal metastatic trials indicate pembrolizumab improves the quality-of-life of patients compared with active monitoring.

Differences in costs in the model are driven by the cost of pembrolizumab and higher subsequent treatment costs in the distant metastases health state in the active monitoring arm. Differences in QALYs gained are largely driven by greater QALYs in the pembrolizumab arm in the disease-free health state. This is because of pembrolizumab increasing the number of years patients spend disease free.

MSD does not believe this indication qualifies for a Severity Modifier as expected QALY loss on SoC vs. the general population does not meet any Severity Modifier threshold.

To address the uncertainties caused by no data from KEYNOTE-091 for the later transitions, a significant number of scenarios were run exploring different cure assumptions, calibration options and alternative curve selections.

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)
As explained in section 2c, there are no additional adjuvant treatments in the established practice available for the subgroup for which MSD is seeking NICE recommendation (early-stage NSCLC patients following complete surgical resection and adjuvant chemotherapy and whose tumours have PD-L1 biomarker expression on less than 50% of their tumour cells). This means that there is still a high chance for the disease to progress to stages where curative treatments are no longer possible. Pembrolizumab would represent a 'step-change' in the management of the condition for this subpopulation, by providing NSCLC patients at early-stage with a treatment plan that reduces the risk of the cancer coming back. Implementation of an immunotherapy would allow shifting of treatment pathways towards earlier preventative treatment enabling more patients to remain disease-free.

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
No equality issues are anticipated.

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.
In oncology clinical trials, the severity of adverse events are usually graded according to US National Cancer Institute's AE Severity Grading Scale - Common Terminology Criteria for Adverse Events (CTCAE). [28] CTCAE can also be used to grade the AE for non-oncology studies, but generally not appropriate for studies using healthy volunteers. • Grade 1 Mild; asymptomatic (no symptoms) or mild symptoms; clinical or diagnostic observations only; no intervention indicated • Grade 2 Moderate; minimal, local or non-invasive medical intervention indicated; limiting age-appropriate instrumental ADL (activities of daily living- explanation in the glossary section) • Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing or feeding).

- Grade 4 Life-threatening consequences; urgent medical intervention indicated.
- Grade 5 Death related to AE.

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

ADL – (activities of daily living) Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.
AJCC – (American Joint Committee on Cancer) collaboration of professional organizations that develop and update cancer staging systems and education.

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:

1. European Medicines Agency (EMA). EMEA/H/C/003820/II/0121. Keytruda European Public Assessment Report (EPAR). Available from: https://www.ema.europa.eu/documents/variation-report/keytruda-h-c-003820-ii-0121-epar-assessment-report-variation_en.pdf. . 2023.
2. Medicines & Healthcare products Regulatory Agency (MHRA). KEYTRUDA® Summary of Product Characteristics. Available from: https://products.mhra.gov.uk/search/?search=keytruda&page=1 [Access Date: 21 February 2024].
3. Cancer Research UK. Lung cancer. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/about. [Access Date: 25 February 2024] [
4. National Lung Cancer Audit (NLCA). NLCA annual report (for the audit period 2018). 2021.

5. Cancer Research UK. Stages and grades of lung cancer. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/stages-grades. [Access Date: 25 February 2024].
6. World Health Organization (WHO). Cancer. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer. [Access Date: 25 February 2024].
7. Cancer Research UK. Cancer incidence statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence [Access Date: 25 February 2024].
8. National Lung Cancer Audit (NLCA). National Lung Cancer Audit (NLCA) – State of the nation report 2023 for patients in England during 2021 and Wales during 2020-2021. Available from: https://www.hqip.org.uk/resource/lung-cancer-ncla-apr23/ . [Access Date: 25 February 2024]. 2023.
9. Cancer Research UK. Cancer mortality for common cancers. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/common-cancers-compared#heading-Zero. [Access Date: 25 February 2024].
10. NHS Digital. Cancer Survival in England, cancers diagnosed 2016 to 2020, followed up to 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-survival-in-england/cancers-diagnosed-2016-to-2020-followed-up-to-2021 [Access Date: 25 February 2024]. 2023.
11. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26(21):3552-9.
12. Birring SS, Peake MD. Symptoms and the early diagnosis of lung cancer. Thorax. 2005;60(4):268-9.
13. National Cancer Institute (NIH). Non-Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version, Clinical Presentation. Available from: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#_48567_toc. [Access Date: 10 October 2023] [
14. Cancer Research UK. Tests for lung cancer. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/getting-diagnosed/tests-for-lung-cancer. [Access Date: 21 February 2024].
15. National Institute for Health and Care Excellence (NICE). Quality standard [QS17] - Lung cancer in adults. 2019.
16. National Institute for Health and Care Excellence (NICE). NICE guideline [NG122]. Lung cancer: diagnosis and management. Last updated: 26 July 2023. 2023.
17. National Institute for Health and Care Excellence (NICE). TA823 - Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta823 . 2022.
18. National Institute for Health and Care Excellence (NICE). TA761 - Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection. Available from: https://www.nice.org.uk/guidance/ta761. 2022.
19. MSD. Data on File. Clinical Engagement.
20. Poghosyan H, Sheldon LK, Leveille SG, Cooley ME. Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: A systematic review. Lung Cancer. 2013;81(1):11-26.
21. Sarna L, Evangelista L, Tashkin D, Padilla G, Holmes C, Brecht ML, et al. Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. Chest. 2004;125(2):439-45.
22. Cancer Research UK. About side effects of chemotherapy. Available from: https://www.cancerresearchuk.org/about-cancer/treatment/chemotherapy/side-effects/about. [Access Date: 21 February 2024].

23. Cancer Research UK. Chemotherapy for lung cancer. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/treatment/chemotherapy-treatment. [Access Date: 21 February 2024].
24. Liu M, Liu L, Zhang S, Li T, Ma F, Liu Y. Fear of cancer recurrence and hope level in patients receiving surgery for non-small cell lung cancer: a study on the mediating role of social support. Supportive Care in Cancer. 2022;30(11):9453-60.
25. Yang X, Li Y, Lin J, Zheng J, Xiao H, Chen W, et al. Fear of recurrence in postoperative lung cancer patients: Trajectories, influencing factors and impacts on quality of life. J Clin Nurs. 2023.
26. Kim SH, Jo MW, Kim HJ, Ahn JH. Mapping EORTC QLQ-C30 onto EQ-5D for the assessment of cancer patients. Health Qual Life Outcomes. 2012;10:151.
27. Emc. KEYTRUDA 25 mg/mL concentrate for solution for infusion. Summary of Product Characteristics and Patient Information Leaflet (PIL). Available from: https://www.medicines.org.uk/emc/product/2498. [Access Date: 21 February 2024].
28. National Institutes of Health (NIH). Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (2017). Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. [Access Date: 27 February 2024].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Clarification questions

April 2024

File name	Version	Contains confidential information	Date
ID3907 Pembrolizumab clarification questions MSD [CON]	1.0	Yes	03/04/2024

Notes for company

Highlighting in the template

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

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

Section A: Clarification on effectiveness data

PD-L1 expression

A1. The results of the KEYNOTE-091/PEARLS trial contradicted clinical expectations, with available data failing to show a statistically significant benefit, at $p < 0.05$, of pembrolizumab within the PD-L1 TPS ≥50% subpopulation. In the CS, it is stated that this is likely to be due to an ‘’overperforming” control arm in the ≥50% subpopulation.

a) Please provide evidence to support the above statement that the control arm in the PD-L1 TPS ≥50% subpopulation overperformed, as opposed to, for example, the control arm in the PD-L1 TPS <50% subpopulation underperforming;

Better-than-expected outcomes have been observed in the control arm of the PD-L1 TPS ≥50% subpopulation with median DFS not reached at IA2 (median follow-up: 32.4 months [range: 0.6 – 68]).[1] This result does not reflect what has been observed in another trial conducted in the adjuvant setting (IMpower010) where at a similar follow-up (32.2 months [IQR: 7.5–38.4]) median DFS for the control arm (best supportive care) was 35.7 months (95%CI: 29.7, NE).[2] The positive outcomes were also confirmed at later follow-up in KEYNOTE-091 (IA3) where median DFS in the placebo group of the PD-L1 TPS ≥50% subpopulation (that received prior adjuvant chemotherapy) was [redacted] months [95%CI: [redacted].[3]

This seems to contradict some evidence on PD-L1 prognostic value showing poorer prognosis in early-stage NSCLC with high PD-L1 expression when not treated with PD-1/PD-L1 inhibitors.[4, 5]

Conversely, similar trends in DFS outcomes are seen in the placebo group of other PD-L1 subpopulations in KEYNOTE-091 compared to Impower010 (median DFS [redacted] months [95%CI: [redacted]] vs 31.4 months [95%CI: 24.0–NE] in KEYNOTE-091 (IA3) and Impower010, respectively, for the PD-L1 1-49% subpopulations; median DFS [redacted] months [95%CI: [redacted]] and 37.0 months [95%CI: 28.6–NE] in KEYNOTE-091 (IA3) vs Impower010, respectively, for the PD-L1 <1% subpopulations).[2, 3]

Although an imbalance in unknown factors (e.g., molecular biomarkers) might have also contributed to the KEYNOTE-091 outcomes in the PD-L1 TPS ≥50% subpopulation, it cannot be excluded that the overperformance of the placebo group led to a less significant benefit of pembrolizumab compared to placebo.

b) The EAG notes the point estimate HRs for DFS are similar between the PDL-L1 TPS <1% subpopulation (HR: 0.75) and PD-L1 TPS 1-49% (HR: 0.70). Given the mechanism of action of pembrolizumab, please comment on whether the company consider PD-L1 TPS to be a meaningful treatment effect modifier/subgroup.

It should be noted that PD-L1 expression (<1% versus 1-49% versus ≥ 50%) was a stratification factor in KEYNOTE-091. KEYNOTE-091 is a large trial with a good sample size in each of these subpopulations that would likely detect a large difference in DFS between the two treatment groups. There is no strong evidence that treatment effect differed between the PD-L1 TPS <1% and 1-49% subgroups. We have acknowledged the uncertainties over the evidence in the PD-L1 TPS ≥ 50% subpopulation for which different results are noted, and proactively restricted the population in which we are seeking reimbursement.

A2. Please provide an estimate of the prevalence of patients with PD-L1 TPS <50% (<1% vs 1-49%) in clinical practice in England. Do you consider the distribution of participants with different PD-L1 TPS expression in the KEYNOTE/PEARLS trial to be representative of patients eligible for pembrolizumab in clinical practice?

The distribution of participants with different PD-L1 TPS expression in the KEYNOTE-091 trial (Table 11 of the CS) is overall consistent with the data from the National Lung Cancer Audit (NLCA) on predictive marker testing in patients with advanced lung adenocarcinoma in England (Table 1).[6].

Similar prevalence data have been reported in a Danish study conducted in consecutive unselected patients with NSCLC (all stages), with 63% (95% CI: 60–67%) and 30% (95% CI: 27–34%) of patients having PD-L1 ≥1% and PD-L1 ≥50% positive cells, respectively.[7] Therefore, we can infer a prevalence of 37% and 33% for PD-L1 <1% and 1-49% expression, which is in line with what observed in the

KEYNOTE-091 trial. Although this study was not conducted in England, little to no difference in expression is expected across regions.[8]

Also, some differences with the evidence provided above can be explained by the tumour stage in which the data were reported as PD-L1 expression has been found to be lower in early-stage NSCLC. [5, 9]

Table 1. Distribution of PD-L1 expression

	KEYNOTE-091 – Prior Adjuvant Chemotherapy Population[a]	NLCA report (2020)[6]	Skov et al., 2020[7]	KEYNOTE-671[10] [b]	Forde et al., 2022[11][c]
TPS <1%	39.2%	33%	37%	34.8%	43.6%
TPS 1-49%	32.7%	24%	33%	32%	28.5%
TPS >=50%	28.1%	38%	30%	33.2%	21.2%

[a] Proportions are reported for all patients in the Prior Adjuvant Chemotherapy Population
[b] Proportions are reported for the pembrolizumab group
[c] Proportions are reported for the nivolumab with chemotherapy group

The resource impact report for atezolizumab recommended by NICE in 2021 as monotherapy for untreated advanced non-small cell lung cancer (TA705), reported 30% of patients diagnosed with stage IV metastatic disease with PD-L1 positive expression of at least 50%.[12]

Moreover, the distribution of PD-L1 expression observed in the KEYNOTE-091 is in line with that reported in other trials conducted in early-stage NSCLC, such as KEYNOTE-671[10] and Checkmate-816 (Forde et al., 2022).[11] Despite the trial setting, the consistency in the prevalence estimates across trials provides some reassurance on the trial representativeness of real-world clinical practice.

Based on the above, no limitations to the applicability of the distribution of the PD-L1 expression to the clinical practice in England are anticipated.

KEYNOTE-091/PEARLS participant characteristics

A3. Clinical experts advising the EAG noted the majority of participants in the KEYNOTE-091/ PEARLS trial were younger than patients in clinical practice in

England, and noted that age as a potential treatment effect modifier due to a lower tolerability of pembrolizumab in older individuals. Please comment on the representativeness of the age of the trial subpopulation of interest to clinical practice in England, and comment on whether age may be a meaningful treatment effect modifier.

Median age of lung cancer patients at diagnosis in England is 73 years. However, this is estimated across all stages, including stage IV where older patients are expected to be identified, also as a result of a late diagnosis. Conversely, a younger cohort of patients is likely to be diagnosed at early stage. It is also important to note that all patients in this population must have been fit enough for surgery and to complete subsequent adjuvant chemotherapy, another factor that suggests they will be younger than the average NSCLC patient.

UK/England-specific evidence on age distribution by stage is sparse and based on single-centre studies. A number of studies have shown a lower median age for patients in the adjuvant setting receiving surgery, also when compared to patients with same stage of NSCLC receiving SABR.[13-16]

Moreover, participants in other trials conducted in early-stage NSCLC for different treatment types, have shown similar age distribution.[10, 11, 17]

Table 2. Median age and age distribution in early-stage NSCLC trials

Trial name	Median Age (range), years	≥65 years, n (%)
KEYNOTE-091[a] (adjuvant)	******	******
KEYNOTE-671[b] (perioperative)[10]	63 (26–83)	176 (44.3)
CHECKMATE-816[c] (neoadjuvant)[11]	64 (41–82)	86 (48.0)
Impower010[d] (adjuvant)[17]	62 (34-77)	45 (39)

[a] Median is reported for all patients in the PD-L1 TPS <50% Subpopulation
[b] Median is reported for the pembrolizumab group
[c] Median is reported for the nivolumab with chemotherapy group
[d] Median is reported for the atezolizumab group in the PD-L1 TC ≥50% Stage II-IIIA population

The DFS subgroup analysis in the PD-L1 TPS < 50% subpopulation in KEYNOTE-091 does not show a different treatment effect across age groups and therefore there is no evidence suggesting that age may be a treatment effect modifier in fit patients with resected NSCLC that receive adjuvant chemotherapy.

Treatment pathway and subsequent therapies

A4. The current treatment pathway, as presented in Figure 3 of the company submission is not consistent with data on subsequent therapies received by participants with distant metastases from the KEYNOTE-091 trial, available from the Statistical Report (example below).

According to Figure 3 of the CS, patients will receive immunotherapy or chemotherapy following distant metastases, whereas in the KEYNOTE-091 trial, a considerable proportion received subsequent radiotherapy and/or surgery. Please comment on this inconsistency and provide an updated figure for the current treatment pathway, if necessary.

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]		[redacted]		[redacted]	
Participants who had any subsequent oncologic therapies for NSCLC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent drug therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent radiation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Participants could have multiple subsequent oncologic therapies for NSCLC.
Every participant is counted a single time for each applicable row and column.
Database Cutoff Date: 24JAN2023

Figure 3 of the CS summarises the type of subsequent treatments that are commonly used in clinical practice in patients with resected early-stage NSCLC when they experience a recurrence at later stage. The table above shows KEYNOTE-091 data on any subsequent therapies that participants with distant metastases received; this includes subsequent radiation or surgery that patients may

have undergone alongside systemic therapy, which is the most common type of subsequent therapy (******%). It should be noted that the subsequent therapies presented above are not mutually exclusive and patients could have received multiple subsequent therapies.

More specifically, of the ****** cases of surgery in the pembrolizumab group, only ****** ****** according to our clinical trials team. This corresponds to ******% of the participants with distant metastasis in the pembrolizumab group. Most of the surgeries were ****** (n=******), which are common in clinical practice, or ****** (n=******) (Table 3).

With regard to subsequent radiation (n=******), most of these procedures targeted ****** (n=******) and ****** (n=******) which suggests a palliative intent. The radiotherapy targeting the ****** (n=******) was also likely to have palliative intent according to our clinical trials team. Palliative radiotherapy is common in clinical practice to treat symptoms arising from the primary cancer or sites of secondary spread (Table 4).

Similar treatment patterns can be observed for the placebo group.

Table 3. Listing of First Subsequent Surgery – Participants With Distant Metastasis as First Event for DFS (Primary Censoring Rule) Based on Investigator Assessment and Who Discontinued or Completed Study Treatment and Received Subsequent Surgery – Overall Population (ITT Population)

	Pembrolizumab, n	Placebo, n
Subsequent surgery	******	******
******	******	******
******	******	******
******	******	******
******	******	******
******	******	******

******Table 4. Listing of First Subsequent Radiotherapy – Participants With Distant Metastasis as First Event for DFS (Primary Censoring Rule) Based on Investigator Assessment and Who Discontinued or Completed Study Treatment and Received Subsequent Radiotherapy – Overall Population (ITT Population)**

	Pembrolizumab, n	Placebo, n
Subsequent radiation	******	******
******	******	******
******	******	******
******	******	******

******	******	******
******	******	******

******The data above suggest that a large proportion of radiation therapies and surgical procedures were likely to have been offered in combination with the main treatment targeting the lung. While time constraints did not allow a detailed interpretation of the subsequent therapies for each participant, the data above do not suggest a substantial deviation from the clinical practice in England.

A5. Priority question. Please provide data both on the first and all subsequent therapies received by participants in the KEYNOTE-091/PEARLS trial (i.e., equivalents of Table 2 and Table 3 from the file "KEYNOTE-091 IA3 Statistical Report - subsequent therapies") for the subpopulation of participants with TPS < 50% following adjuvant chemotherapy for:

a) Participants With Locoregional Recurrence for Disease-free Status (Primary Censoring Rule) Based on Investigator Assessment;

Data on the first and all subsequent therapies received by participants with Locoregional Recurrence for the subpopulation of participants with TPS < 50% following adjuvant chemotherapy (PD-L1 TPS < 50%) are presented below.

Table 5. Summary of First Subsequent Oncologic Therapies – Participants With Locoregional Recurrence for Disease-free Status (Primary Censoring Rule) Based on Investigator Assessment – PD-L1 TPS < 50% Subpopulation (All-Participants-as-Treated Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	******	******	******	******	******	******
Participants who had any subsequent oncologic therapies for NSCLC	******	******	******	******	******	******
First Subsequent Chemoradiation	******	******	******	******	******	******
First Subsequent Drug Therapy	******	******	******	******	******	******
First Subsequent Radiation	******	******	******	******	******	******
First Subsequent Surgery	******	******	******	******	******	******

Every participant is counted a single time for each applicable row and column.
Subsequent chemoradiation includes participants who received drug therapy and radiotherapy concurrently or sequentially as first subsequent regimen.
Subsequent systemic therapy includes participants who received drug therapy as first subsequent therapy after and do not fulfil the criteria for subsequent chemoradiation.
Subsequent radiotherapy includes participants who received radiotherapy as first subsequent therapy.
Subsequent surgery includes participants who received surgery as first subsequent therapy.
Database Cutoff Date: 24JAN2023

Table 6. Summary of Subsequent Oncologic Therapies – Participants With Locoregional Recurrence for Disease-free Status (Primary Censoring Rule) Based on Investigator Assessment – PD-L1 TPS < 50% Subpopulation (All-Participants-as-Treated Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	******	******	******	******	******	******
Participants who had any subsequent oncologic therapies for NSCLC	******	******	******	******	******	******
Subsequent drug therapy	******	******	******	******	******	******
Subsequent radiation	******	******	******	******	******	******
Subsequent surgery	******	******	******	******	******	******

Participants could have multiple subsequent oncologic therapies for NSCLC.
Every participant is counted a single time for each applicable row and column.
Database Cutoff Date: 24JAN2023

b) Participants With Distant Metastases for Disease-free Status (Primary Censoring Rule) Based on Investigator Assessment.

Data on the first and all subsequent therapies received by participants with Distant Metastases for the subpopulation of participants with TPS < 50% following adjuvant chemotherapy (PD-L1 TPS < 50%) are presented below.

Table 7. Summary of First Subsequent Oncologic Therapies – Participants With Distant Metastases for Disease-free Status (Primary Censoring Rule) Based on Investigator Assessment – PD-L1 TPS < 50% Subpopulation (All-Participants-as-Treated Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	******	******	******	******	******	******
Participants who had any subsequent oncologic therapies for NSCLC	******	******	******	******	******	******
First Subsequent Chemoradiation	******	******	******	******	******	******
First Subsequent Drug Therapy	******	******	******	******	******	******
First Subsequent Radiation	******	******	******	******	******	******
First Subsequent Surgery	******	******	******	******	******	******

Every participant is counted a single time for each applicable row and column.
Subsequent chemoradiation includes participants who received drug therapy and radiotherapy concurrently or sequentially as first subsequent regimen.
Subsequent systemic therapy includes participants who received drug therapy as first subsequent therapy after and do not fulfil the criteria for subsequent chemoradiation.
Subsequent radiotherapy includes participants who received radiotherapy as first subsequent therapy.
Subsequent surgery includes participants who received surgery as first subsequent therapy.
Database Cutoff Date: 24JAN2023

Table 8. Summary of Subsequent Oncologic Therapies – Participants With Distant Metastases for Disease-free Status (Primary Censoring Rule) Based on Investigator Assessment – PD-L1 TPS < 50% Subpopulation (All-Participants-as-Treated Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	******	******	******	******	******	******
Participants who had any subsequent oncologic therapies for NSCLC	******	******	******	******	******	******
Subsequent drug therapy	******	******	******	******	******	******
Subsequent radiation	******	******	******	******	******	******
Subsequent surgery	******	******	******	******	******	******
Participants could have multiple subsequent oncologic therapies for NSCLC. Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 24JAN2023						

Results in Table 8 for the PD-L1 TPS < 50% subpopulation are consistent with those reported for the overall population (table provided by EAG in question A4), with the exception of subsequent radiation which occurred less frequently in the pembrolizumab group of the PD-L1 TS < 50% subpopulation.

Prior adjuvant chemotherapy

A6. Please provide a summary of participants' exposure to prior adjuvant chemotherapy for the subpopulation whose tumours express PD-L1 with <50% TPS, including, the most common agents used and tabulated data equivalent of Table 15, in the CS.

The median duration of exposure to prior adjuvant chemotherapy in the PD-L1 TPS < 50% subpopulation was similar in both treatment groups (Table 9).

Table 9. Summary of Exposure to Prior Adjuvant Chemotherapy – PD-L1 TPS < 50% Subpopulation (ITT Population)

	Pembrolizumab (N=363)	Placebo (N=363)
Duration on Therapy (days)		
Mean	******	******
Median	******	******
SD	******	******
Range	******	******
Number of Cycles		
Mean	******	******
Median	******	******
SD	******	******
Range	******	******
Database Cutoff Date: 24JAN2023		

The most common (>10% of participants) agents used in the pembrolizumab group compared with placebo were cisplatin/vinorelbine (******% vs ******%), carboplatin/vinorelbine (******% vs ******%), and carboplatin/paclitaxel (******% vs ******%).

Table 10. Participants With Prior Adjuvant Chemotherapy (Incidence > 0% in One or More Treatment Groups) – PD-L1 TPS < 50% Subpopulation (ITT Population)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	363		363		726	
with one or more prior adjuvant chemotherapy	363	(100.0)	363	(100.0)	726	(100.0)
with no prior adjuvant chemotherapy	0	(0.0)	0	(0.0)	0	(0.0)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS						
ANTINEOPLASTIC AGENTS	**363**	**(100.0)**	**363**	**(100.0)**	**726**	**(100.0)**
ANTINEOPLASTIC AGENTS	******	******	******	******	******	******
CARBOPLATIN;DOCETAXEL	******	******	******	******	******	******
CARBOPLATIN;ETOPOSIDE	******	******	******	******	******	******
CARBOPLATIN;GEMCITABINE	******	******	******	******	******	******
CARBOPLATIN;PACLITAXEL	******	******	******	******	******	******
CARBOPLATIN;PEMETREXED	******	******	******	******	******	******
CARBOPLATIN;VINORELBINE	******	******	******	******	******	******
CISPLATIN;DOCETAXEL	******	******	******	******	******	******
CISPLATIN;ETOPOSIDE	******	******	******	******	******	******
CISPLATIN;GEMCITABINE	******	******	******	******	******	******
CISPLATIN;PACLITAXEL	******	******	******	******	******	******
CISPLATIN;PEMETREXED	******	******	******	******	******	******
CISPLATIN;VINORELBINE	******	******	******	******	******	******

Every participant is counted a single time for each applicable specific prior adjuvant chemotherapy. A participant with multiple prior adjuvant chemotherapy within a medication category is counted a single time for that category. Each specific prior adjuvant chemotherapy is listed under all relevant medication classes based on the medication's generic name, regardless of route of administration or reason for use.

A medication class or specific medication appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Database Cutoff Date: 24JAN2023

Outcomes

A7. Clinical experts advising the EAG highlighted that a benefit in disease-free survival (DFS) does not necessarily predict a benefit in overall survival (OS). Given that DFS is used to predict OS in the model, please provide further evidence on the relationship between DFS and OS in early NSCLC.

The modelled relationship between DFS and OS makes clinical sense; an economic model structure where OS depends to a large degree on DFS has been used in

several NICE technology appraisals in early lung cancer and our own model structure was validated as appropriately capturing the natural history of the disease by 12 UK clinicians across two advisory boards. MSD consider that factors that might influence differential post-recurrence survival, such as the differential use of subsequent treatments between the arms, have been captured in the economic model.

One other immunotherapy trial has formed the basis of a NICE technology appraisal in adjuvant NSCLC. In addition to KEYNOTE-091 (DFS and OS HRs = 0.72 [0.58-0.89] and 0.73 [0.55-0.97]) in the submitted population) there is IMpower010 in which the DFS and (now reported longer term) OS HRs in the reimbursed population (PD-L1>50%) are 0.43 (0.27-0.68) and 0.43 (0.23-0.78) after 5 years of follow-up.[18]

A8. DFS was a composite outcome that could include: presence of disease at baseline, death, locoregional recurrence, distant metastasis, both locoregional recurrent and distant metastasis, and new malignancy. The EAG notes the incidence rate of each of these event types may differ across the follow-up period. Please provide a cumulative incidence plot of each event type throughout the follow-up period separately for pembrolizumab treated patients and placebo treated patients:

a) In the Prior Adjuvant Chemotherapy Population (ITT Population);

b) In the PD-L1 TPS < 50% Subpopulation (subgroup of the Prior Adjuvant Chemotherapy Population ITT Population).

Due to time constraints, cumulative incidence plots are provided for the main components contributing to the overall proportion of DFS events (locoregional recurrence, distant metastasis, both locoregional recurrent and distant metastasis). The tail of these curves should be interpreted with caution due to the lower number of patients at risk. Cumulative incidence of DF→ LR and DF→DM were also provided in Appendix N of the CS (Figures 13-16 of CS).

Figure 1. Cumulative Incidence Function of Disease-Free Survival (Primary Censoring Rule): Locoregional Recurrence - Prior Adjuvant Chemotherapy Population (ITT Population)

Locoregional Recurrence includes both those participants who are recorded as "Local and/or Regional Recurrence" as well as those participants experiencing "New Malignancy". All other DFS components are treated as competing risks.
Database Cutoff Date: 24JAN2023

Figure 2. Cumulative Incidence Function of Disease-Free Survival (Primary Censoring Rule): Distant Metastasis - Prior Adjuvant Chemotherapy Population (ITT Population)

[redacted]

Distant Metastasis includes both those participants who are recorded as "Distant Metastasis" as well as those participants experiencing both "Distant Metastasis" and "Local and/or Regional Recurrence" on the same date. All other DFS components are treated as competing risks.
Database Cutoff Date: 24JAN2023

Figure 3. Cumulative Incidence Function of Disease-Free Survival (Primary Censoring Rule): Locoregional Recurrence - PD-L1 TPS < 50% Subpopulation (ITT Population)

[redacted]

Locoregional Recurrence includes both those participants who are recorded as "Local and/or Regional Recurrence" as well as those participants experiencing "New Malignancy". All other DFS components are treated as competing risks.
Database Cutoff Date: 24JAN2023

Figure 4. Cumulative Incidence Function of Disease-Free Survival (Primary Censoring Rule): Distant Metastasis - PD-L1 TPS < 50% Subpopulation (ITT Population)

[redacted]

Distant Metastasis includes both those participants who are recorded as "Distant Metastasis" as well as those participants experiencing both "Distant Metastasis" and "Local and/or Regional Recurrence" on the same date. All other DFS components are treated as competing risks.
Database Cutoff Date: 24JAN2023

A9. The EAG notes that, among the patients with distant metastasis events, there was a numerically larger proportion of brain lesions in placebo-treated patients compared to pembrolizumab-treated patients. A clinical advisor to the EAG noted that the timing of the occurrence of brain lesions would aid in interpreting these data. Please provide a cumulative incidence plot of the occurrence of brain lesions over the follow-up period separately for patients treated with placebo and those treated with pembrolizumab.

Cumulative Incidence plot of the occurrence of brain metastasis in the pembrolizumab and placebo group is shown in Figure 5.

As the number of participants at risk reduces beyond month 60, the tail of the curves should be interpreted with caution. Nevertheless, to the extent that any inference can be drawn from this graph, the shape of the curves appears to be consistent with pembrolizumab having a preventive effect on brain metastases. This is supported by the plateau emerging after approximately 3 years where very few events are observed in either arm.

Figure 5. Cumulative Incidence Function of Disease-Free Survival (Primary Censoring Rule): Brain Metastasis – PD-L1 TPS < 50% Subpopulation (ITT Population)

[redacted]

Note: Brain Metastasis includes both those participants who recorded "Brain" as location for "Distant Metastasis" as well as those participants with recorded "Brain" as location for "Distant Metastasis" coinciding with a "Local and/or Regional Recurrence" on the same date. All other DFS components are treated as competing risks.
Database Cutoff Date: 24JAN2023

A10. DFS and OS were analysed using Cox Regression assuming proportional hazards. For each analysis:

a) Please provide an assessment of the degree to which proportional hazards holds for the DFS and OS analyses using diagnostic plots;

b) Please comment on the interpretability of the estimated HRs and likely direction of any bias resulting from any meaningful violations of proportional hazards.

Results of testing for proportional hazards for DFS and OS, including Schoenfeld residual plots, are presented below (Table 11-Table ***12***; Figure 6Figure ***7***). Based on the statistical testing (p-values > 0.1) and visual assessment of the plots, there is no obvious evidence supporting rejection of the assumption that hazards are proportional over time.

Table 11. Summary of testing for proportional hazards for DFS

Chisq	df	p-value
******	******	******
******	******	******

Figure 6. Schoenfeld residual plot (DFS)

[redacted]

Table 12. Summary of testing for proportional hazards for OS

Chisq	df	p-value
******	******	******
******	******	******

Figure 7. Schoenfeld residual plot (OS)

[redacted]

A11. Please provide a plot of the underlying DFS hazard over time for both the pembrolizumab arm and placebo arm in KEYNOTE-091/PEARLS.

The DFS hazard over time for both the pembrolizumab arm and placebo arm is presented below. It should be noted that as the number of patients at risk decreases at later time points, the uncertainty of hazard estimates increases, as demonstrated by the wide confidence interval at later timepoints in the pembrolizumab group.

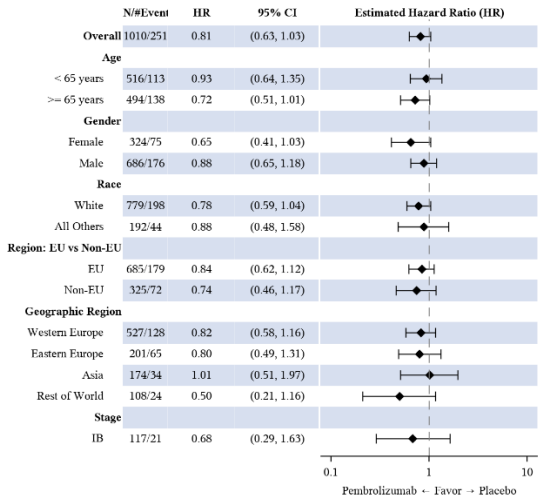
Figure 8. DFS Hazard rate over time for pembrolizumab

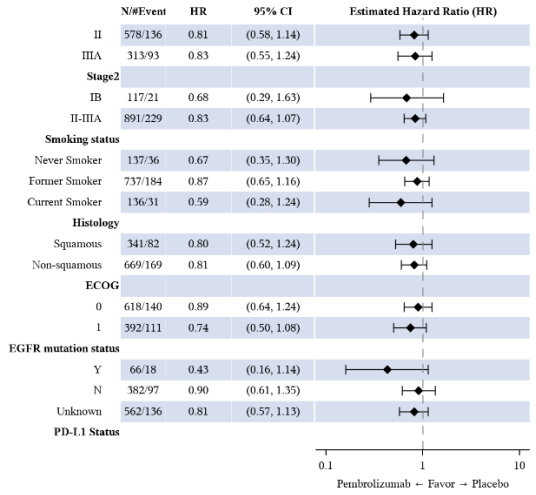
Figure 9. DFS hazard rate over time for placebo

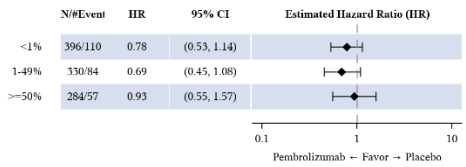
A12. Subgroup analyses have only been presented for DFS and not OS. Please provide a subgroup analysis despite the company stating that “Subgroup analyses were planned to compare DFS and OS by treatment arm in the stratification factors and additional demographic variables”. Please provide OS subgroup analyses for these variables in the prior adjuvant chemotherapy subpopulation, by non-PD-L1 subgroup factors and PD-L1 subgroup factors.

The OS subgroup analysis for the Prior Adjuvant Chemotherapy population is presented below (Figure 10). It should be noted that OS data are still immature (113 [22.3%] and 138 [27.4%] OS events observed in the pembrolizumab and placebo group, respectively) with median not being reached in either treatment groups in any of the subgroups. This adds further uncertainties to the exploratory nature of this analysis.

Figure 10. Forest Plot of OS Hazard Ratio - Prior Adjuvant Chemotherapy Population (ITT Population)







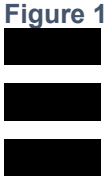
1. For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment, adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥ 50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), using Wald confidence interval. For other subgroups, analysis is based on Cox regression model with treatment as a covariate using Wald confidence interval.
2. If a subgroup variable has two levels and one level of the subgroup meets any criteria below, then this subgroup variable will not be displayed: (1) if the number of participants in a category of a subgroup variable is less than 50, (2) the number of events in a category of a subgroup variable is zero in one treatment arm, (3) the number of events in a category of a subgroup variable is less than 5 in the pooled arms.
Database Cutoff Date: 24JAN2023

A13. Subgroup analyses have not been provided for the subpopulation in which approval is sought (PD-L1 TPS <50% following adjuvant chemotherapy). The EAG acknowledges the company's statement that, "the small sample size of the subgroups would result in wider confidence intervals and no meaningful conclusions could be drawn about the treatment effect in these subgroups". However, the EAG

notes that the size of the subgroups will differ for each variable, and notes that some meaningful analyses are likely possible. Please present the results of the DFS and OS subgroup analyses within the subgroup for which approval is being sought, including the PD-L1 subgroups <1% and 1-49%.

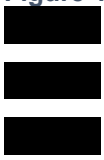
The DFS and OS subgroup analysis for the PD-L1 TPS < 50% subpopulation are presented in Figure 11 and Figure 12. The DFS and OS benefits of pembrolizumab over placebo were consistent across the majority of prespecified subgroups and with the results in the subgroups of the Prior Adjuvant Chemotherapy population (Figures 8 and 9 of the CS and Figure 10). Caution should be taken when interpreting these results due to the exploratory nature of this analysis, particularly in those subgroups which are not stratification factors, and for the OS endpoint, due to the early time of the analysis.

Figure 11. Forest Plot of DFS Hazard Ratio – PD-L1 TPS < 50% Subpopulation (ITT Population)



1. For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment, adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥ 50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), using Wald confidence interval. For other subgroups, analysis is based on Cox regression model with treatment as a covariate using Wald confidence interval.
2. If a subgroup variable has two levels and one level of the subgroup meets any criteria below, then this subgroup variable will not be displayed: (1) if the number of participants in a category of a subgroup variable is less than 50, (2) the number of events in a category of a subgroup variable is zero in one treatment arm, (3) the number of events in a category of a subgroup variable is less than 5 in the pooled arms.
Database Cutoff Date: 24JAN2023

Figure 12. Forest Plot of OS Hazard Ratio – PD-L1 < 50% Subpopulation (ITT Population)



1. For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment, adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥ 50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), using Wald confidence interval. For other subgroups, analysis is based on Cox regression model with treatment as a covariate using Wald confidence interval.
2. If a subgroup variable has two levels and one level of the subgroup meets any criteria below, then this subgroup variable will not be displayed: (1) if the number of participants in a category of a subgroup variable is less than 50, (2) the number of events in a category of a subgroup variable is zero in one treatment arm, (3) the number of events in a category of a subgroup variable is less than 5 in the pooled arms.
Database Cutoff Date: 24JAN2023

A14. Please provide a list of all subgroups that were prespecified in the trial protocol and/statistical analysis plan for KEYNOTE-091.

a) Please reference the page numbers of the protocol/statistical analysis plan where each of the subgroups are pre-specified;

Information on pre-specified subgroups analysis can be found in section 16.1.9.2 Supplemental Statistical Analysis Plan (sSAP) of the IA3 CSR (page 2423).

Subgroup analyses were planned to compare DFS and OS by treatment arm in the stratification factors:

- **stage** (IB versus II versus IIIA)
- **PD-L1 IHC expression** (0% versus 1-49% versus ≥ 50%)
- **adjuvant chemotherapy** (no chemotherapy vs. adjuvant platinum-based chemotherapy)
- **region** (Western Europe versus Eastern Europe versus Rest of the world versus Asia).

In addition, subgroup analyses by **histology** (squamous versus non-squamous), **smoking status** (former/current smokers versus non-smokers), **sex** (female versus male), **age** (<65 versus ≥65 years), **baseline ECOG performance status** (0 versus 1), **race** (White versus non-White), **geographic region** (EU versus Ex EU) were also planned.

Subgroup analysis by **smoking status** (former smokers versus current smokers versus non-smokers) and **EGFR mutation status** (Yes versus No versus Unknown) were also considered at protocol stage.

b) Please confirm whether the subpopulation in which approval is sought (PD-L1 TPS <50% following adjuvant chemotherapy) was a pre-specified subgroup in the KEYNOTE-091A;

We confirm that the PD-L1 TPS <50% following adjuvant chemotherapy subpopulation was not a pre-specified subgroup. Please note that, as explained in the response to question a), adjuvant chemotherapy and PD-L1 TPS 0% versus 1-49% versus ≥ 50% are stratification factors and pre-specified subgroups.

c) If the subpopulation in which approval is sought (PD-L1 TPS <50% following adjuvant chemotherapy) was not a pre-specified subgroup, please comment on the risk of bias associated with a data-driven decision to focus on a *post-hoc* subgroup.

Pembrolizumab received the Marketing Authorisation for the treatment in patients who had previously received adjuvant chemotherapy. Even though this indication represents a subgroup of the overall population, adjuvant chemotherapy was a stratification factor and a pre-specified subgroup analysis, which, from a statistical perspective, strengthened the result in this subgroup.

Despite the PD-L1 TPS <50% not being a stratification factor, no substantial imbalances in the baseline characteristics are found between treatment arms. This can most likely be ascribed to PD-L1 <1% and 1-49% being stratification factors. The only exceptions are smoking, ECOG, histology and ALK status which appeared imbalanced in the overall population as well, mainly due to them not being stratification factors. However, no concerns were raised by the CHMP during regulatory assessment as the baseline characteristics were considered balanced between treatment arms.[1]

The above considerations should provide some reassurance on the robustness of the results in the subpopulation in which we are seeking a NICE recommendation.

While the general limitations of a *post-hoc* subpopulation are acknowledged, it is important to note that the choice of focusing on the PD-L1 TPS <50% following adjuvant chemotherapy subpopulation was not data-driven; instead, it reflects the subpopulation in the adjuvant setting with no adjuvant treatment options beyond chemotherapy available, while taking into account the level of certainty and validity of the evidence. The KEYNOTE-091 results in the PD-L1 TPS <1% and 1-49% subgroups do not currently warrant a further restriction in the proposed subpopulation, which aims to address the totality of the patient group with high unmet medical need.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model so that these can be combined. Furthermore, if the company chooses to update its base-case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base-case assumptions are provided with the response along with a log of changes made to the company base-case.

KEYNOTE-091 updated base-case

We would like to thank the EAG for providing their suggestions for our economic analysis. As agreed during the clarification questions call, we have updated the base-case in line with the following changes in our model assumptions and inputs as summarised in Table 13. We have also referenced where these are found in our clarification questions response and commented on the impact of these changes to the updated base-case. Updating these changes brings our ICER from ******/QALY gained to ******/QALY gained. When running the EAG's suggested scenario analyses, we will be using the term 'updated base-case' from this point hereafter to assess the magnitude of difference.

Table 13. Updated base-case inputs for the KEYNOTE-091 economic model

Reference in clarification questions	Description of change	Impact on ICER? (Large, small, none)
B20.	Changed the general population utility values from Ara et al. to Hernández Alava et al. 2022	Small decrease
B23.	Corrected the source description for pre-progression utility of 0.743 within the model	None

B31.	Reduced the active 2L treatments in DM by 10%, the remainder to receive no active treatment (Source_Market Shares)	Small decrease
B35. And B39	B35. Added CT scan resource use i.e. 2 per year for the disease-free (DF) weekly resource use up to year 5 in 'Raw – HCRU!' sheet cell I48 B.39. Updated CT scan resource use from 42% 4 times a year to 82% every year in the local-regional recurrence weekly resource use in 'Raw – HCRU!' sheet cell O48	Small increase
B37.	Corrected the cost of radiotherapy from £5,557 to £4,517.	Small increase
B41.	Updated adverse event cost per event to include all complications and comorbidities for all relevant HRG codes.	Small increase

Population

B1. The target patient population is stated to be adults with NSCLC who have undergone complete surgical resection after adjuvant chemotherapy and whose tumours have PD-L1 TPS <50%. Despite this the company uses the whole trial population to inform the baseline characteristics in the model. Please provide a scenario using the baseline characteristics of the target population from the trial.

We have provided a scenario with the baseline characteristics from the PD-L1 <50% TPS subpopulation as summarised in the below table:

Table 14.Updated baseline characteristics from KEYNOTE-091 for PD-L1 <50% TPS subpopulation

Characteristic	As applied in CS	As applied in CQs	Source

	Overall	PD-L1 <50%	
Starting age (years), mean	64.3 years	****** years	KEYNOTE-091
Percentage female (percentage)	31.7%	******	
Body surface area (m^2), mean	1.9	******	
Body surface area (m^2), standard error	0.01	******	
Weight (kg), mean	74.8	******	
Weight (kg), standard error	0.5	******	
Glomerular filtration rate (GFR) (ml/min/1.73m^2)	75.0	75.0	NICE TA181

Applying the PD-L1 <50% baseline characteristic in the model resulted in an ICER of ******/QALY gained.

B2. As noted in clarification question A3 participants in the KEYNOTE-091/ PEARLS trial was younger than patients in clinical practice in England.

a) If available, please source data from UK clinical practice and provide a scenario using baseline age of patients in the target population.

b) If this data is unavailable, please provide a scenario using baseline age from the SEER-Medicare Cohort.

Please see the response to question A3 for more details on part a).

For the request in part b) it should be noted that the minimum age to qualify for Medicare in the US is 65 years. As such, the distribution of patients within this database is truncated by eligibility. Removing all patients aged under 65 from a normally distributed cohort with mean ****** and SD=****** years, as in the PD-L1<50% group in KEYNOTE-091, results in a residual mean of 71 years (based on 10,000 iterations in MS Excel), which is more comparable to the mean age at surgery in SEER-Medicare (73.5 years). Rather than KEYNOTE-091 not being generalisable to clinical practice, it is likely that both studies are reasonably reflective of surgical patients seen in practice but that SEER-Medicare has an age restriction.

Disease Free Survival

B3. Priority question: The difference in disease-free survival between placebo and adjuvant pembrolizumab provides an indication of the proportion of patients in which surgery with curative intent was not successful and adjuvant treatment has been beneficial. As such, for these disease-free patients, the treatment effect of adjuvant pembrolizumab may wane over time (i.e. the risk of recurrence in the DF health state for adjuvant pembrolizumab may decline over time to match placebo).

a) **Please provide a range of scenarios that test the impact on the ICER if the treatment effect of adjuvant pembrolizumab wanes over time and patients revert to the disease trajectory of patients on routine surveillance (convergence of DFS curves). Consider scenarios which incorporate waning from year 4 onwards (that is, 3 years after stopping treatment at 1 year).**

b) **The trial DFS data, shown in figure 5 and table 18 of the submission, indicates the gap between pembrolizumab and placebo peaks prior to 30 months and then closes. The trial OS data, shown in figure 6 and table 22 of the submission, indicate the gap between pembrolizumab and placebo peaks prior to 48 months and then closes. Given this would constitute evidence for waning in the relative treatment effect, can the company please explain why they believe, "there is no clear indication of a waning of treatment effect in either outcome"?**

Part a): MSD note that while NICE committees have often imposed treatment waning assumptions on pembrolizumab indications in metastatic solid tumour settings, they have not imposed them in early-stage indications (TA766, TA837 and TA851). Given that these assumptions are entirely evidence-free in any setting, the company considers it most appropriate to follow the precedent established in TA766, TA837 and TA851 of no treatment waning. Please refer to section B.3.3 of the CS where the considerations around treatment waning are described in detail. It is very important to note that the hazards between the arms are equalised by the cure assumption anyway and there is no/very little residual treatment effect after this time depending on the assumed cure proportion. We suggest that the effect of imposing treatment

effect waning be explored by moving cure assumptions a year earlier i.e. beginning the process of equalising hazards at year 4. The company imposed the cure assumption from years 4-6 in a scenario which slightly decreased the base case ICER.

Part b): The company consider that this would be a strong conclusion to draw based on visual inspection of the tails of the KM curves. We note that DFS patients have fewer routine follow-up appointments later in the study, which naturally results in more censoring as time goes on. Examination of the N-at-risk tables (Raw_KM curves (subgroup) tab in the model) shows that approximately 33% of the DFS population and 40% of the OS population as estimated by the KM curves have been censored by 30 months and 48 months respectively. With longer follow-up, a more accurate assessment of the change in hazards over time will be possible. Please also see the company's response to clarification question A10 which includes formal statistical tests against the proportional hazards assumption and Shoenfeld residual plots that find no evidence of non-proportionality of hazards over time.

B4. Priority question: In the executive summary of the advisory board, it is stated that, "A conservative approach should be taken and the treatment effect should be capped at 5 years (i.e. the end of the observed follow-up period)". However, as the cure is implemented as a linear reduction in risk progressing to 95% between years 5-7, an ongoing treatment benefit is retained by pembrolizumab after 5 years.

a) **Please justify why the clinical experts' advice has been disregarded.**

This statement is from the 2023 Clinical Advisory Board, and the advisers were referring only to the calibration of the downstream transition probabilities to match OS from KEYNOTE-091 (please see page 21 of the 2023 Clinical Advisory Board Executive Summary) and not to the cure point. Rather than disregarding the advice on capping the calibration, we chose to augment it to match the 5-7 year approach that had been taken with the cure assumption. The cure point of 5-7 years was also derived from discussions at the 2022 Clinical Advisory Board among other sources (please see section B.3.3.1 of the CS) but when imposed in the model this resulted in a visual kink in the DFS curve. In order to make the change in DFS hazards less abrupt, we chose to gradually increase the cure

proportion between 5-7 years in the base case, which was an approach suggested as appropriate by the clinicians at the 2022 advisory board.

While there is significant precedent for a cure point of around 5 years being assumed in health economic models in early NSCLC, the evidence supporting the time point at which the calibration cap should be imposed is not strong, and so the company consider a hard stop at 5 years or a gradual cap from 5-7 years to be equally plausible. A hard stop at 5 years has the advantage that it was suggested by the clinical advisers and represents the most conservative approach i.e. it matches the observed data and projects no further, but has the disadvantage that it imposes a sudden change in hazards, which has less biological plausibility.

b) Provide a scenario where the treatment effect is equalised at 5 years.

This scenario can be achieved by setting all relevant calibration and cure points to '5' on the Specifications tab of the model and results in an ICER of [redacted].

B5. Priority question: In line with table 19 of the TA761 submission for osimertinib, please provide scenarios using parametric mixture cure models.

a) Provide the long-term survival rates predicted by the MCM for each curve,

b) Provide goodness of fit statistics for DFS using MCMs.

Table 19 of the TA761 submission includes a series of MCM models using the *flexsurvcure* function in R[19], which are used to validate the cure proportion assumed on standard care in the economic model for that appraisal. We have replicated TA761's table 19 here (with the exception of the 5-year DFS column, which would be uninformatively uniform for KEYNOTE-091 given the length of follow-up). The company consider mixture-cure modelling to be a less suitable approach for modelling a cure fraction in cases like resectable NSCLC where the natural history of the disease is well known and maximal follow-up from the trial is close to the point at which clinicians agree by consensus that curative-intent treatment has been successful (typically 5 years, although this may be slightly longer in this cohort, as in our 5-7 year base case). Nonetheless, the company notes that the proportion of

patients who are DF at 7 years in the base case model's control arm is 31% which is similar to the cure fractions estimated by the various parametric options within the *flexsurvcure* package.

Table 15. Cure fractions as per *flexsurvcure* package

MC Model	AIC	Cure fraction
Exponential	2246.142	******
Weibull	2244.359	******
Log-normal	2258.991	******
Log-logistic	2247.327	******
Gamma	2244.349	******
Generalisex Gamma	2246.343	******
Gompertz	2247.068	******

B6. Priority question: The original submission to use the 95% reduction in risk was in the adjuvant treatment of HER2-positive early breast cancer (TA569). The EAG used the 95% cured rate in conjunction with a 36-month cure point in order to obtain a 10-year recurrence rate in line with the 1.08% seen in Takeuchi *et al*. 2009. Given this value was produced specifically for the model and HER2-positive early breast cancer, please update the estimate of the cure related reduction in risk value using Sonoda *et al.* 2019, which provides data for NSCLC, or a more relevant alternative source?

Thank you for this helpful suggestion. We were unable to search for and critically appraise the long-term literature in the time available so examined Sonoda et al 2019[20] as suggested. This study presented data on ultra-late recurrence among 1,458 Japanese patients receiving resection with curative intent between 1990 and 2006. The authors state that 12/1,458 (0.8%) patients had an "ultra late recurrence", which was a recurrence occurring between 10.1 and 19.8 years after resection. We compared this to the difference in the sum of the DF->LR and DF->DM cumulative incidence curves between 10.1 and 19.8 years in the economic model's Markov traces under base case settings and noted that a total 0.73% of control arm patients and 0.77% of pembrolizumab patients were predicted to have a recurrence of NSCLC during this time interval. Taken at face value, these data appear very similar to the data reported in Sonoda et al 2019. We would note, however, that obtaining long term epidemiological data that are applicable to the decision problem is very

challenging; techniques for diagnosis, staging and resection of NSCLC (e.g. PET-CT, EBUS-TBNA and VATS) have evolved a great deal since the 1990s and loss to follow up in very long term studies is always an issue.

In relation to question B4, we would also note that the authors of Sonoda et al mention that 5-years DFS is conventionally considered the "cure point" in resected NSCLC, which is in line with the various sources discussed in section B.3.3.1 of the CS.

B7. Priority question: The company states that parametric proportional hazards models with piecewise fittings were used by the company using a 1-year cut-point.

a) **Why was 1 year selected as the cut-point?**

The decision was based on maximum treatment duration being 1 year rather than any examination of the survival curves to locate a natural "break point" or similar technique.

b) **Please explore these curves with a 3-year cut-point and a 1-year and 3-year cut-point.**

The company has explored this suggestion but our interpretation is that this does not add anything valuable to the very extensive set of survival analyses already available within the model and discussed in the CS. We would also note that using a piecewise model with a break at 3 years means that the data after the cut-point are informed by comparatively little data.

The following new dropdown menu has been added to the "Specifications" tab to enable scenario analyses using a 3-year cut-point under efficacy estimation approach #3:

- "Under Approach 3, allow treatment effect to differ between the following time periods:"
    - Option 1 (original cut-point): Before and after 1 year
    - Option 2 (requested cut-point): Before and after 3 years

The parameter estimates corresponding to the Option 2 are added in the "Raw_Param Estimates" tab.

Under Approach 3 Option 2, there are 9 unique combinations of parametric functions for transitions from the DF state. To assess the impact of using this alternative cut-point under Approach 3, we repeated the same selection process as originally performed to select the base-case combination of parametric functions out of the 67 candidate combinations, but replaced the 9 combinations under Approach 3 Option 1 with the 9 combinations under Approach 3 Option 2. The tables below show the mean squared errors (MSEs) and DFS and OS predictions in each arm for the 9 combinations under Approach 3 Option 2 (prior to any calibration to optimize fit with observed OS).

Overall, the combinations under Approach 3 Option 2 did not outperform the selected base-case combination (Approach 1/log-normal/log-normal), but generally demonstrated better statistical fit than the same combinations under Approach 3 Option 1. Among the 9 combinations under Approach 3 Option 2, six combinations were excluded poor visual and/or statistical fit in one or both arms, and one combination (Approach 3/Gompertz/Gompertz) was excluded due to early convergence of the OS curves. There are thus two finalist combinations under Approach 3 (Weibull/Gompertz and exponential/Gompertz) that warrant inclusion as scenario analyses when using a 3-year cut-point under Approach 3; the same two combinations were also identified as finalists when using a 1-year cut-point under Approach 3.

The 1-year and 3-year cut-point was further not explored as the current model considers an extensive range of combinations of parametric functions, with multiple plausible combinations of distributions that produced a close fit with observed DFS from KEYNOTE-091 in both arms.

Table 16. Comparison of different parametric models used to estimate DFS and OS, under Approach 3 with 3-year cut point: Pembrolizumab

Rank by MSE *(out of all 67 combinations under approaches 1-3)*	Parametric functions		MSE vs. observed DFS	Predicted DFS (%)						Predicted OS (%)					
	DF → LR	DF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs

6	Gompertz	Weibull	0.0001977																			
9	Weibull	Weibull	0.0002137																			
11	**Weibull**	**Gompertz**	**0.0002191**																			
12	Exponential	Weibull	0.0002207																			
13	Gompertz	Gompertz	0.0002227																			
14	**Exponential**	**Gompertz**	**0.0002246**																			
54	Gompertz	Exponential	0.0004281																			
56	Weibull	Exponential	0.0005463																			
58	Exponential	Exponential	0.0005739																			

Table 17. Comparison of different parametric models used to estimate DFS and OS, under Approach 3 with 3-year cut point: Placebo

Rank by MSE *(out of all 67 combinations under approaches 1-3)*	**Parametric functions**		**MSE vs. observed DFS**	**Predicted DFS (%)**						**Predicted OS (%)**					
	DF → LR	**DF → DM**		**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**	**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**
10	Gompertz	Gompertz	0.0005735												
20	**Weibull**	**Gompertz**	**0.0008545**												

										[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	**Exponential**	**Gompertz**	**0.0008941**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
37	Gompertz	Weibull	0.0011683	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	Weibull	Weibull	0.0016217	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
53	Exponential	Weibull	0.0016792	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
57	Gompertz	Exponential	0.0024659	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
63	Weibull	Exponential	0.0032802	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65	Exponential	Exponential	0.0033918	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3

c) **Please explore the use of 1, 2 and 3 knot splines to model DFS.**

We were unable to implement c) in the time available but we note that we have provided a very large number of survival curves to select from and consider that the curves used in the base case and in scenario analyses fit the observed data well. The company believes that the use of the additional flexibility offered by splines would not be supported by guidance in TSD21; not only do more standard parametric competing risks survival curves provide an adequate fit to the data, which suggests even more flexible modelling is not needed, but spline modelling is likely to be harder to interpret in a competing risks framework where the timing of the knots will differ for each type of risk in each arm. We note that the competing risks models already represent a form of flexible modelling and one that has been accepted as

appropriate in multiple previous NICE TAs of immunotherapy used in early cancer settings (TA837, TA766, TA830).

B8. Please provide fit statistics for all DFS curves provided.

We have provided weighted MSE for all the DFS curves provided. Traditional AIC and BIC statistics are not available for composite outcomes drawn from multiple competing risks curves.[21]

B9 Please provide the r code used to fit the DFS models.

We were unable to assemble this in the time available. Standard packages were used. If the EAG have any queries about particular analyses we can look into these in greater detail.

B10. Clinical experts have advised the EAG that even patients who remain disease free will experience a mortality rate 50-60% higher than the general population. Please provide the option to apply a SMR to disease free patients.

An SMR option has been added to the Life Tables tab in the economic model. Setting the SMR to 1.5 results in a moderate increase to the ICER [redacted]/QALY gained). The company would be interested in whether this suggestion was based on recent empirical evidence or not. It is important to note that only 95% of patients are assumed to be cured after 5-7 years meaning NSCLC recurrence is still possible across the time horizon of the model, which will already account for some proportion of this suspected elevation in mortality. For example, when comparing the per-cycle all-cause mortality probability in the middle of year 15 in the model (e.g. by comparing OS between cycle 754 and 755; prob=0.0012) to the general population all cause per cycle mortality probability in year 15 in the Life Tables tab (prob=0.0008), the SMR is already approximately 1.5. The company's preference is not to utilise the additional SMR functionality given the lack of cited empirical evidence on what an appropriate SMR would be and the fact that the model is already accounting for elevated mortality versus a general population cohort.

Local recurrence

B11. Priority question: Please provide the option in the model to select the other external sources, shown in figure 12, to inform LR transition rates.

There was not time to incorporate these data in the model but the weekly rate data for the other sources are available in table 39 of the CS and may be inputted manually to examine these scenarios.

B12. Priority question: The baseline age of the SEER medical cohort was 73.5. The baseline age in the model is 64.3 with most local recurrence happening within the first 5 years. How is it possible that the SEER data is overpredicting OS for placebo, to the point of requiring recalibration, when the demographics suggest it should be dramatically underpredicting OS?

The answer to this question is complex as several parameters influence OS and not just the SEER-Medicare ER data that were used to inform the LR health state transitions. The first thing to note is that in a completely uncalibrated model (i.e. option 1 is selected in the box at Effectiveness!I144 and the DM adjustment factor is switched off at I192) placebo OS is predicted reasonably well (See Figure 13 below).

Figure 13. Predicted OS vs. observed OS in KEYNOTE-091 and SEER-Medicare (prior to real-world adjustment of DM->Death based on SEER-Medicare and prior to calibration) *****

The second thing to note is that OS in SEER was the highest among all data sources identified and shown to the advisers at the 2023 clinical advisory board. While SEER-Medicare was selected as the most appropriate based on the patient characteristics, OS outcomes were much better than those used in the TA823 model (Nakamichi et al 2017) and others shown to the advisers (table 39 in the CS). The advisers considered that although SEER-Medicare was the most representative source based on patient characteristics, the data looked optimistic based on their experience. It is therefore plausible that, despite the older baseline age of the cohort, outcomes observed in this dataset overestimate what would be seen in practice and that the calibrated data are more plausible.

B13. As identified by the company, the SEER data transition rates from LR to DM provides the lowest transition rates of all sources, yet it was selected due to

clinicians stating the patient characteristics were the most applicable. Given these data requires calibration (increasing LM->death/DM) to fit with the trial data would the other sources uncalibrated not be more appropriate? It is common for real-world-evidence to have different outcomes compared to trial data. If available, consider obtaining alternative trial data as a source.

The completely uncalibrated economic model reproduces the trial OS data well in the placebo arm, which suggests the data sources used for LR->DM and DM->Death may be reasonable. The issue necessitating calibration is that the model underpredicts OS in the pembrolizumab arm. We are not aware of any trial that would supply the differential downstream transition probabilities that are required for the model to reproduce observed OS.

Distant metastatic recurrence

B14. Priority question: The company uses KEYNOTE-189, KEYNOTE-407 and Ramalingam *et al.* (2020) & Soria *et al.* (2018) to inform OS in the DM arm.

a) **Please produce a table showing the baseline characteristics of these trials compared to KEYNOTE-091.**

These data are available in the relevant publications. With apologies to the EAG, we ran out of time to create a summary table. It is important to note that inferences drawn between the baseline characteristics of patients in the metastatic setting and those in the adjuvant setting must be drawn with extreme caution. Data from KEYNOTE-189/-407 are applied to patients with metastatic recurrence in the economic model, whose baseline characteristics (e.g. performance status) are likely to be different to the baseline characteristics at study enrolment in KEYNOTE-091.

b) **Please provide the clinical study reports from these additional KEYNOTE studies.**

We can confirm that there are no clinical study reports for the latest analyses from KEYNOTE-189 or KEYNOTE-407. Follow-up data from these trials were not pre-specified in the protocols and were generated for the purposes of publications in the literature i.e. Garassino et al. (2023) and Novello et al. (2023). Therefore, these publications contain the latest OS from KEYNOTE-189 and KEYNOTE-407 respectively to inform the DM arm.

c) Were the patients in the KEYNOTE-189 and -407 studies treatment naive to pembrolizumab?

Yes. Prior exposure to immunotherapy was an exclusion criterion in both trials.

d) If yes, is this likely to be a source of bias in using this data to inform the pembrolizumab retreatment effectiveness?

It is possible that this is a source of bias but the direction and magnitude of the bias is not known. The patients in question within the economic model have had at least 18 months of DFS prior to any recurrence. According to the Markov trace from the model, the median time to recurrence among this late recurring group is 3.25 years (Trace_AdjReg2, columns AF:AG, row 93 onwards in the model). It might be reasonable to assume that patients treated with pembrolizumab who experienced several years disease free and then were retreated with pembrolizumab had a worse prognosis than those enrolled in the KEYNOTE-189 and –407 studies but then the converse might also be true. This is because this patient group are more closely followed up and their metastatic disease would likely be diagnosed at a relatively earlier stage than a *de novo* patient. We consider it possible that even if prior exposure to pembrolizumab in the adjuvant phase were predictive of lower efficacy, which is unknown, that doesn't necessarily mean that the retreated patients in the economic model have shorter survival than those in the DM studies because their baseline prognosis might be better.

B15. Priority question: The EAG acknowledges that re-treatment with pembrolizumab for distant metastases was included in the model due to the committee for TA823 expressing that re-challenge would be permitted. In order for the committee in the current appraisal to have adequate information available for decision making, please also include a scenario in which re-treatment with pembrolizumab in the DM health state is not permitted.

The company considers that this is not a matter of committee judgement but the confirmed pathway in UK clinical practice. Rechallenge with anti PD1/PD-L1 immunotherapy for recurrent disease following successful completion of initial treatment and at least a 6-month period without disease recurrence or progression is commissioned by NHS England in a number of indications.[22] Nevertheless, the

model already includes the functionality to examine whether retreatment is allowed or not and to vary the exclusion time on the Specifications worksheet.

B16. Priority question: The calibration factor applied to DM -> death transitions, in order to have OS match the trial data, results in the transition rate to death for IO ineligible patients in the pembrolizumab arm to be lower than placebo patients who will be actively treated with immunotherapies. This seems clinically implausible.

a) **Please can the company justify why patients that are ineligible for treatment with an IO therapy after adjuvant pembrolizumab have a higher OS compared to patients receiving IO therapy after adjuvant placebo.**

MSD agree that taken at face value these data appear incongruous. It is important to note that the rapidly progressing patients represent a special subset of the patients in the trial. They may have already had occult metastases or disease with a rapidly progressing natural history. It is possible, therefore, that at the time of diagnosis of metastatic disease, the placebo patients might be relatively more advanced whereas the pembrolizumab patients could have already benefitted from the disease modifying effects of immunotherapy and might temporarily have better outcomes. We note that there is little evidence available from the trial to support these hypotheses (but please refer to section 3.3.2 of the CS where supportive evidence for calibration from the literature is discussed in detail) although the proportion of DM patients with brain metastases appeared numerically higher in the placebo arm. The next important factor to bear in mind is that, because the downstream transition probabilities must be calibrated to replicate the outcomes observed in the trial, some residual benefit for pembrolizumab must have been observed within the trial time horizon, although the precise mechanisms for why such data were observed are not well understood. They do not appear to be related to any generalisability issues.

b) **Please provide an option to not calibrate the I/O ineligible patient arm.**

MSD have provided this option on the Effectiveness tab in row 150. When holding the TPs for the I/O ineligible group constant and re-running the calibration algorithm, this has the expected result that there is very little effect on the ICER but that the

difference in the other downstream transition probabilities between the arms must increase to compensate.

B17. Priority question: Please provide a scenario using parametric models, based on appropriate trial data, to inform the DM->Death transition rate (similar to how DFS has been modelled).

We interpret this request to mean implementing time-dependent downstream transition probabilities in the Markov model. While we understand that it is conceptually reasonably to consider that the DM->Death state would have time-dependent transition probabilities, this is highly computationally complex to implement in a Markov model where patients are both arriving and exiting the state in every cycle. The unknown extent and direction of bias in these parameters (see response to B14d) also makes the added precision of this approach less desirable versus considerations around complexity and transparency. Overall, we consider that it is more appropriate to vary these parameters in sensitivity analyses rather than seeking to more precisely match the data observed in DM clinical trials.

B18. Costs for 1L and 2L metastatic treatment are bundled together so patients do not transition from one to the other. Please discuss whether this will lead to the cost discounting being inappropriately applied?

It is likely that discounting is applied to these costs too early by an average of mean PFS time (approximately a year in the placebo arm of the economic model). The company considers the limitation that 2L subsequent treatment costs are overestimated by approximately 3.5% in each arm to be minor. This is because 2L subsequent treatments are inexpensive, only accounting for around 4% of DM treatment costs and the limitation applies to both arms equally. We quickly investigated this by reducing the subs treatment costs on rows 112:113 of the Market Shares tab in the model by 3.5% and the ICER increased by only a few pounds.

Intervention

B19. Scenario 7 presented in Table 68 of the CS is intended to show results for pembrolizumab given Q6W. However, this was only implemented in the adjuvant setting, whereas in the metastatic setting Q3W dosing was still assumed.

a) What is the rationale for this decision?
b) Please present a scenario where Q6W is implemented consistently for pembrolizumab.

The rationale for this decision is that DFS patients in the adjuvant setting are considered to be cured until evidence to the contrary is found. Clinicians are therefore happier to see them less frequently than in the metastatic setting. Scenario 7 applied the Q6W regimen only to the adjuvant setting, which generated an ICER of ******. Applying the Q6W dosing to both the adjuvant and metastatic setting generated an ICER of ****** gained which increases the ICER but only marginally. This updated scenario including Q6W regimen in both adjuvant and metastatic settings has a comparatively lower ICER versus the Q3W regimen (i.e. the base case). This difference can be explained by the total administration costs for pembrolizumab being lower in the Q6W regimen versus the Q3W regimen, given the number of cycles per treatment is lower i.e. ****** versus ****** respectively. In clinical practice, pembrolizumab is typically initiated Q3W in the metastatic setting as clinicians prefer to monitor patients more closely, once response and tolerability have been established, they consider moving patients to Q6W. The true administration costs are therefore likely to be somewhere between the two. Overall, it is possible that costs arising from a scenario that models Q6W in the adjuvant setting and Q3W in the metastatic setting presents a reasonable middle-ground although the reality may be more of a mix in both settings.

Health-related quality of life

B20. Priority question: For the general population utility values, the NICE methods guide recommends using the Health Survey for England (HSE) 2014 dataset, as recommended by the DSU (Hernández Alava *et al.* 2022). Please

update the general population utility values used for age adjustment in the model to use the HSE 2014 dataset.

Thank you for this suggestion, we have incorporated the HSE 2014 dataset by Hernández Alava et al. 2022 in the model which can be found in the 'Utility' tab of the model and updated the base-case to reflect this. The previous dataset used in the model, Ara et al. (2010) is also included as an option to allow for comparison.

B21. Priority question: In the CS, it states that in KEYNOTE-091, EQ-5D-3L questionnaires were filled in during patient visits every 12 weeks during the first year after randomization (starting on day 1 of visit 1); every 6 months during the second year and then yearly until year five.

a) **Please provide details on the number of patients and number of responses measured at each time point as well as overall patient numbers informing the utility values for each health state.**

Table 18. Compliance Rates for EQ-5D by Timepoint Disease-Free (Primary Censoring Rule) Based on Investigator Assessment and Without g1+ Adverse Event – Overall Population (PRO FAS Population)

Study: KEYNOTE 091[a]	Completed/Expected to complete questionnaires (% Compliance)	
	Pembrolizumab (N[b] = 529)	Placebo (N[b] = 543)
Baseline	******	******
Week 12	******	******
Week 24	******	******
Week 36	******	******
Week 48	******	******
Week 74	******	******
Week 100	******	******
Week 152	******	******
Week 204	******	******
Week 256	******	******

a: Database Cutoff Date: 24JAN2023

b: Number of participants: PRO FAS population, participants without adverse event and who were disease-free based on investigator assessment during at least one visit and were expected to complete the EQ-5D questionnaire.

Expected to complete questionnaires at each time point include all participants who do not have missing data due to a missing by design reason.

Compliance is the proportion of participants who completed the PRO questionnaire among those who are expected to complete at each time point, excluding those missing by design.

Table 19. Compliance Rates for EQ-5D by Timepoint Locoregional Recurrence (Primary Censoring Rule) Based on Investigator Assessment – Overall Population (PRO FAS Population)

Study: KEYNOTE 091[a]	Completed/Expected to complete questionnaires (% Compliance)	
	Pembrolizumab (N^b = 95)	Placebo (N^b = 111)
Week 12	******	******
Week 24	******	******
Week 36	******	******
Week 48	******	******
Week 74	******	******
Week 100	******	******
Week 152	******	******
Week 204	******	******
Week 256	******	******

a: Database Cutoff Date: 24JAN2023

b: Number of participants: PRO FAS population, participants with locoregional recurrence based on investigator assessment during at least one visit and were expected to complete the EQ-5D questionnaire.

Expected to complete questionnaires at each time point include all participants who do not have missing data due to a missing by design reason.

Compliance is the proportion of participants who completed the PRO questionnaire among those who are expected to complete at each time point, excluding those missing by design.

Table 20. *Compliance Rates for EQ-5D by Timepoint Distant Metastases (Primary Censoring Rule) Based on Investigator Assessment – Overall Population (PRO FAS Population)*

Study: KEYNOTE 091[a]	Completed/Expected to complete questionnaires (% Compliance)	
	Pembrolizumab (N^b = 109)	Placebo (N^b = 149)
Week 12	******	******
Week 24	******	******
Week 36	******	******
Week 48	******	******
Week 74	******	******
Week 100	******	******
Week 152	******	******
Week 204	******	******
Week 256	******	******

a: Database Cutoff Date: 24JAN2023

b: Number of participants: PRO FAS population, participants with distant metastases based on investigator assessment during at least one visit and were expected to complete the EQ-5D questionnaire.

Expected to complete questionnaires at each time point include all participants who do not have missing data due to a missing by design reason.

Compliance is the proportion of participants who completed the PRO questionnaire among those who are expected to complete at each time point, excluding those missing by design.

Table 21. EQ-5D Health Utility Scores by Disease-free Status (Primary Censoring Rule) Based on Investigator Assessment United Kingdom Mapping Algorithm - Overall Population (Full Analysis Set Population)

Disease-free Status	Pembrolizumab (N=578)					Placebo (N=581)					Total (N=1159)				
	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI	n†	m‡	Mean	SE	95% CI
Disease-free	[redacted]														
Disease recurrence	[redacted]														
Locoregional recurrence	[redacted]														
Distant metastases	[redacted]														
Not disease-free at baseline	[redacted]														

n† = Number of participants with non-missing EQ-5D score.
m‡ = Number of records with non-missing EQ-5D score.
EQ-5D score during baseline is excluded.
Summary statistics are computed based on several records per participant treated as independent observations.
Database Cutoff Date: 24JAN2023

b) **In the CS, the number of patient visits informing each health state was stated as follows: n= 5,273 in the disease free (no AE) health state, n= 463 in the local-regional recurrence health state and n=595 in the distant metastases health state. Please clarify if these are the total number of patient visits for each health state or the number of patient visits in which EQ-5D-3L values were measured, given that ED-5D was not measured in every patient visit. If they represent the former, please provide the number of patient visits used to inform the health state utility values.**

These are the total number of visits in which EQ-5D was measured.

B22. Priority question: In TA830 (pembrolizumab for adjuvant treatment of renal cell carcinoma), utility values from KEYNOTE-564 were derived from a linear mixed-effects model with patient-level random effects, with the justification that the approach was used to account for the correlation among repeated measures within an individual.

a) **Please explain why use of mixed-effect regression models (as was used in TA830) was not explored in the current appraisal and justify why descriptive analyses of EQ-5D data from KEYNOTE-091 were considered more appropriate.**

As a number of trial subjects had multiple EQ-5D-3L assessments collected for a given health state, repeated measures adjustment was considered for the analysis. Repeated measures adjustment can impact both the estimated mean and variance within an analysis as they effectively downweight values for subjects with multiple measurements, relative to those with a single measurement. If within-individual measurements are positively correlated, this increases the variance due to perceiving there to be “less information” than if all measures were treated as independent. However, whereas traditional repeated measures adjustment approaches are appropriate for many applications involving health data, they generally assume that the number of measures available per subject is not

correlated with the value of the measure of interest. When such correlation is present, biased estimates of the sample mean can result.

In the case of oncology trials, however, a number of correlations are typically present. For instance, compared to trial subjects with multiple measurements, subjects with only a single or fewer measurements for a given health state are more likely to have:

- Died shortly following (e.g., from disease-free state)
- Transitioned to another worse health state (e.g., LR to DM)
- And to have relatively lower utilities within the health state than patients with repeated utility assessments, due to:
    - Being near to the point of transition to a worse health state.
    - Having older age, greater co-morbidities, worse functional status, etc. which correlates with, or contributes to, the transition.

Furthermore, in the context of health economic modelling of the trial population, patients with multiple measurements spending longer time in a health state *should* receive proportionately greater weight for their health utilities than those with a single or fewer measurements, as they account for relatively more of the time and QALYs spent in that state within the model and are more representative of that health state experience. Thus, in the context of oncology trials, providing relatively greater weight to the observations of individuals with a single trial measurement for a health state through repeated measures adjustment can serve to downwardly bias estimated mean values for the health state.

Descriptive analyses, without adjustment, weight utility measurements in proportion to the number of measurements observed in each health state for each patient such that patients with longer time in a health state, and more measurements, receive greater weight than an individual in the health state for a short time and with only a single measurement.

While this does not directly address the issue of appropriate estimation of the variance when repeated measures are present, there are a few mitigating factors which suggest this to be a lesser or non-issue. First, improvements in the estimation

of the mean and the variance with repeated measures approaches are likely to be more pronounced with smaller sample sizes, and when within-patient variability in values for a health state is low compared to inter-patient variability. As previously described, within-patient health state values are expected to decline as patients approach a point of transition to a worse health state and not to remain fixed. As relates to sample size, if say only 8 subjects have data for a health state, with 6 reporting one measurement, 1 two measurements and 1 eight measurements, a repeated measures approach can ensure the last patient does not dominate the results when estimating a mean and variance. However, as is more typical for Oncology trial health states, if there are larger sample sizes of 50 to 500 patients, each with say 1 to 4 measurements for a health state, the impact of within-patient correlation on the estimation of the overall mean value and estimate variability around that mean, relative to if each measurement were to have come from a different patient, is likely to be very low. The present model therefore uses a descriptive approach to analyse health state utilities. Nevertheless, to avoid underestimating the uncertainty around each utility input, the trial-based standard error of each mean health state utility estimate was doubled for the purposes of conducting deterministic and probabilistic sensitivity analyses.

b) **Please provide EQ-5D utility values for each health state (including disease-free with grade 1-2 AEs) in the model using appropriate mixed-effect regression models. Please ensure to fully describe the approach to the regression model, including reasons for inclusion of variables and final specification of the models.**

The company would like to reiterate the arguments in section B.3.4.1 of the CS; 70% of EQ-5D forms were collected in year 1 but most DF life years are accrued to patients who are not on treatment and who are many disease-free years downstream from having invasive surgery. As such, it is the value without any AEs that is the most appropriate to reflect the DF cohort across the time horizon of the model. We also suggest, for the reasons listed in part a), that the descriptive means approach is the most reasonable in this case. An analysis where DF utilities are drawn from all patients without g3+ AEs in year 1 and then from all patients without g1+ AEs in year 2 onwards might be reasonable. An additional point is that EQ-5D is

0.804 at baseline i.e. a few weeks after surgery and immediately after chemotherapy. It is reasonable to expect the average DF EQ-5D score to increase over time as the cohort becomes enriched by the fitter and more genuinely disease-free patients who have long recovered from radical treatment.

Alternative utility values for the disease-free (without toxicity), local-regional recurrence, and distant metastases prior to any subsequent progression (pre-progression distant metastases) are summarised in Table 22. At each visit where health state was assessed, the corresponding EQ-5D-3L score was used to characterise utility. Patient-visits with missing EQ-5D-3L responses were excluded from the analysis. Consistent with the rationale given in the base-case of the CS, there was no utility for post-progression distant metastases derived from KEYNOTE-091. This is because the KEYNOTE-091 trial did not differentiate between pre-progression and post-progression in the DM health state as the trial only captured first recurrence after the DF state.

Table 22. alternative health state utility values using repeated measures approach

Health state	Utilities		Sources
	Value	SE	
Disease-free (without g3+ AEs)	0.801	(0.005)	KEYNOTE-091 (regression approach)
Disease-free (without g1+ AEs)	0.811	0.006	KEYNOTE-091 (regression approach)
Local-regional recurrence	0.765	(0.012)	KEYNOTE-091 (regression approach)
Distant metastases (pre-progression)	0.712	(0.011)	KEYNOTE-091 (regression approach)

Linear mixed-effects models with patient-level random effects were used to account for the correlation among repeated measures within an individual. Two regression specifications were used: i) one for disease-free without grade 3+ AEs and disutility related to grade 3+ AEs and the second for ii) local-regional recurrence and distant metastases. Both specifications incorporated patient-level random effects and the dependent variable of both models was EQ-5D-3L utility score:

- Disease-free (without grade 3+ AEs) and disutility related to grade 3+ AEs - The first regression specification was fitted to patient-visits with a utility

measurement that occurred during each patient's recurrence-free period (N=1,156 patients, with 6,742 unique patient-visits). Independent variables included binary indicators for the presence/absence of grade 3+ AE(s) at each patient visit.

- Local-regional recurrence and distant metastases – the second specification was fitted using all patient-visits with a utility measurement (N=1,158 patients, with 7,810 unique patient-visits). Independent variables included categorical indicators which correspond to health state at a given patient-visit (disease-free, local-regional recurrence, or distant metastases). This regression did not include a covariate for presence/absence of grade 3+ AE(s) so that the utility values for the LR and DM states would incorporate any AE-related disutility in those states (rather than representing utility values for LR and DM without grade 3+ AEs). This was considered appropriate, given that the model only applies separate AE-related disutility in the adjuvant setting and does not apply separate AE-related disutilities for subsequent treatments in the LR and DM states.

B23. In the CS, Table 50, it is stated that the DM pre-progression utility value is from KEYNOTE-091. However, in the model the source of the DM pre-progression utility is given as KEYNOTE-189 & KEYNOTE-407 (pooled). Please confirm which source is correct.

The distant metastases pre-progression utility value of 0.743 is based on the KEYNOTE-091 trial as described in Table 50 of the CS. The pooled KEYNOTE-189 and KEYNOTE-407 utility source applies to the distant metastases for the post-progression utility only. MSD have corrected this source information in the updated model.

B24. Please justify using KEYNOTE-189 & KEYNOTE-407 to inform the distant metastases (post-progression) health state. Please discuss the suitability of the approach with reference to the heterogeneity in patient populations between studies.

Pembrolizumab + chemotherapy is the standard of care for mNSCLC patients with PDL1<50% in the UK and KEYNOTE-189/407 are the key RCTs that underpin regulatory and HTA approval in the non-squamous and squamous populations respectively. PD-L1 expression was a stratification factor in both trials and the data

for the PD-L1<50% subpopulations were used to be consistent with the population in this appraisal. Baseline characteristics are available in the response to question B14a. There are no obvious generalisability concerns. As discussed in the response to B14a, the direction and extent of bias arising from using trials in *de novo* metastatic patients to represent outcomes in recurrent patients is unknown.

Base case results

B25. Priority question: Please provide the base case results (including any revisions based on the EAG's clarification questions), DSA, PSA and scenarios with the assumed discount of 60% for osimertinib excluded.

Table 23. Base-case results (without osimertinib discount)

Technologies	Total costs (£)	Total QALYs	Total LYs	Incremental costs (£)	Incremental QALYs	Incremental LYs	ICER vs. comparator (£/QALY)
Pembrolizumab	[redacted]	[redacted]	9.08				
Placebo	[redacted]	[redacted]	7.98	[redacted]	0.93	1.10	[redacted]

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

Table 24. Disaggregated base-case results (without osimertinib discount)

Costs (£)	Pembrolizumab	Placebo	Incremental (Pembrolizumab vs. Placebo)
Costs, total and by category	[redacted]	[redacted]	[redacted]
Adjuvant treatment costs	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in LR state	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]

Drug administration costs	[redacted]	[redacted]	[redacted]
Radiotherapy costs	[redacted]	[redacted]	[redacted]
Salvage surgery costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in DM state	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Costs, total and by state	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Death (one-time terminal care costs)	[redacted]	[redacted]	[redacted]

Effectiveness	Pembrolizumab	Placebo	Incremental (Pembrolizumab vs. Placebo)
Quality-adjusted life years (QALYs), total and by state	[redacted]	[redacted]	**0.93**
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
AE-related disutility	[redacted]	[redacted]	[redacted]
Age-related disutility	[redacted]	[redacted]	[redacted]
Life years (LYs), total and by state	**9.08**	**7.98**	**1.10**
Disease-free	7.10	5.89	1.21
Local-regional recurrence	0.63	0.54	0.09
Distant metastases	1.35	1.55	-0.20
Incremental outcomes (adjuvant pembrolizumab vs. comparator)			
Incremental costs (£)	-	-	[redacted]
Incremental QALYs	-	-	0.93
Incremental LYs	-	-	1.10
Incremental costs per QALY gained	-	-	[redacted]
Incremental costs per LY gained	-	-	[redacted]

Administration costs

B26. Priority question. In the CS, Table 55, only the administration cost for SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance was presented. However, in the model other administration costs are implemented including, SB13Z: Deliver more Complex Parenteral Chemotherapy at First Attendance, SB15Z: Deliver Subsequent Elements of a Chemotherapy Cycle and SB11Z: Deliver Exclusively Oral Chemotherapy.

a) **Please describe in more detail the administration costs included in the model for treatments in the locoregional recurrence and distant metastases health state. In particular, please clarify why the number of subsequent IV administrations for (nab)-paclitaxel was always assumed to be 2.**
b) **Please clarify why the HRG code SB12Z was used for all simple IV administration costs and SB13Z for all complex IV administration costs instead of using HRG code SB15Z: Deliver Subsequent Elements of a Chemotherapy Cycle for subsequent simple and complex IV administrations.**
c) **Administration costs from the NHS payment scheme 2023/25 are available (https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/). Please provide a scenario that uses the NHS payment scheme 2023/25 administration costs in the model. Additionally, use HRG code SB15Z for all subsequent (i.e. after the first administration) IV simple and complex administrations.**

Part a) Although listed as an option, nab-paclitaxel is not in use in the UK or in this model. Consistent with UK clinical practice, paclitaxel is used instead for the KEYNOTE-407 regimen. The model has been adapted from a global cost-effectiveness model and as such, only a small number of the systemic therapy options that are included in the model are actually in use in this analysis. The cost of the relevant administration code (SB12Z [simple regimens], SB13Z [complex regimens] or SB11Z [oral regimen]) is multiplied by the mean number of cycles from Flatiron real world data (Appendix O in the CS) in the case of the metastatic

regimens or subsequent treatment data from KEYNOTE-091 in the case of the loco-regional recurrence regimens. Mean cycles are available in the Tx Duration tab.

Part b) SB12Z is the standard code that is used for IV I/O monotherapy in NICE technology appraisals, for example TA823, TA766, TA837, TA357, TA366, TA531, TA830. It is not clear to the company what "subsequent elements of a chemotherapy cycle" means in this context and whether this refers to a type of chemotherapy where multiple elements are given within a cycle. For pembrolizumab monotherapy there are no "subsequent elements" per cycle so it is not clear that this applies. Additionally, it is not clear why this cost would be higher than the first attendance costs represented by SB12Z and SB13Z. There are some regimens in the 'Drug & Admin Costs' tab (row 263 onwards) where SB15Z is applied (e.g. nab-paclitaxel) but these regimens are not in use in the UK or in the model and so this does not affect the ICER.

Part c) to the company's knowledge the most recent NHS reference costs are considered to be the standard source for costs in NICE technology appraisals. An advantage of the NHS reference costs is that it reflects costs that have actually been incurred inclusive of trim points, exclusions and weightings. Using the linked payment scheme data to review all the costs in the model would have been very challenging within the available time and would have represented a significant departure from precedent so the company has not done this.

Subsequent treatment costs

B27. Priority question. The EAG has investigated the unit costs of subsequent treatments in the eMIT database and considers the company has not implemented the least expensive options. As NICE requires that the least expensive option for treatments are used in the model, please update the following costs in the model:

Name and pack size	Unit cost	Required dose in the model	Required vials	Cost per dose (including wastage)
Pemetrexed 1 g powder for solution for injection vials (generic) / Packsize 1	£15.24	950 mg	1	£15.24

Carboplatin 600 mg/60 ml solution for infusion vials / Packsize 1	£21.54	600 mg	1	£21.54
Cisplatin 100 mg/100 ml solution for infusion vials / Packsize 1	£9.53	190 mg	2	£19.05

The unit costs for all drug unit costs were sourced from the latest eMIT costs at the time of the submission. MSD note since the submission date, the eMIT database has been updated (as of 5th April 2024). Table 25 summarises the least expensive option (per mg cost) for pemetrexed, carboplatin and cisplatin from the April 2024 update. We would like to note the cost for pemetrexed and cisplatin do not match the unit costs the EAG have suggested (this may be due to the EAG's unit costs being based on the previous edition of the eMIT database which MSD no longer have access to). In the April 2024 edition for carboplatin, we found that the least expensive (per mg) cost was for the 450mg/45ml pack size (consistent with the strength per vial used in the model) which differs to the 600mg the EAG have suggested. We would also like to correct the EAG's required dosing of cisplatin in the model as summarised in the above table, which should be 143mg rather than 190mg. We have assessed the updated unit costs using the EAG's and our findings from the April 2024 edition in scenario analyses. For the scenario with the EAG's preferred unit costs, this generated an ICER of £[redacted]/QALY gained and using the April 2024 unit costs, this generated an ICER of £[redacted]QALY gained.

Table 25. Updated unit costs for pemetrexed, carboplatin and cisplatin

Name and pack size	NPC code	Unit cost (weighted average from eMIT April 2024 edition)	Required dose in the model
Pemetrexed 1 g powder for solution for injection vials (generic) / Packsize 1	DEI021	£11.04	950 mg
Carboplatin 450 mg/45 ml solution for infusion vials / Packsize 1	DHE002	£48.09	600 mg
Cisplatin 100 mg/100 ml solution for infusion vials / Packsize 1	DHA010	£29.27	143 mg

B28. Priority question. Please describe the market share data assumed for subsequent treatment assumed in the locoregional recurrence health state, as presented in tab "Market share", cells E16:I20, as this is not presented or described in the CS.

The section titled "Loco-regional recurrence health state entry costs" in section B.3.5.2. describes this data, albeit somewhat obtusely. The costs in table 58 are split across two separate tabs in the economic model; the Market Shares tab, which includes systemic therapy costs and the HCRU tab, which includes the surgery and radical radiotherapy elements. Both types of costs accrue "one-off" upon entry into the LRR health state. In the Market shares tab, 60% of patients are assumed to get chemotherapy (vinorelbine+cisplatin); 30% are getting chemotherapy alone and the remaining 30% are receiving it as part of a chemo-radiotherapy regimen. The remaining 40% do not get chemotherapy although the majority of these patients receive repeat surgery or radical radiotherapy alone.

B29. Priority question. The company has assumed that all first-line targeted subsequent treatment costs for distant metastases are based on osimertinib. However, osimertinib is only for patients with an EGFR mutation. The company acknowledges the approach is biased (page 101 of the CS). Additionally, drug acquisition costs are a large proportion of the total costs for the distant metastases health state. As such, please update the market share data for first-line targeted metastatic treatment and estimate a weighted cost of first-line targeted therapy for distant metastases based on data for patients with each type of mutation (EGFR, KRAS G12C, ALK and ROS-1 positive) and the appropriate targeted treatment for the mutation and implement this as a scenario.

Unfortunately, this request could not be completed in the time available. It is very important to note firstly that these treatments only apply to a small percentage of people and usage would not differ between the arms of the model. Secondly, for this scenario to affect the ICER, the treatments mentioned would have generate very significant amounts of net health benefit (NHB) versus the surrogate treatment, osimertinib. We suggest that this uncertainty is handled via sensitivity analysis. For example, increasing the company's base case assumed discount of 60% for osimertinib to 100%, dramatically (and in our view implausibly) increasing the level of

NHB generated by TKIs, increases the ICER only about ******/QALY. So while the company acknowledges the approach of using osimertinib costs and outcomes as a surrogate for all targeted treatments introduces bias, it is important to note that the direction of the bias is unknown. This is because it is equally plausible that the other TKIs, which typically have much weaker evidence bases than osimertinib [e.g. single arm trials] are less cost-effective than osimertinib and therefore generate less NHB rather than more. If they would be, on average, less cost-effective than osimertinib then the company's model is biased against pembrolizumab because avoiding progression to DM has been undervalued. The most important point is that, as illustrated by the extreme sensitivity analysis above, the maximum amount that this bias could increase or decrease the ICER is small.

B30. Priority question. The EAG's clinical experts outlined that at second line the majority of patients would be treated with docetaxel rather than pemetrexed + platinum. As a scenario, please assume that 60% of patients are treated with docetaxel and 40% receive no active treatment.

This scenario results in an ICER of ******/QALY gained. A slight increase versus the updated company base case.

B31. Priority question. In the model, second line treatment and administration costs appear to be simply added to first-line treatment costs as a one-off cost when patients enter the distant metastases state. Though 40% of patients in the model receive no active treatment second-line, this appears to be based on clinical advisors stating "*around 30–40% of patients*" would receive best supportive care only at this stage. The model does not seem to account for patients who will not survive to receive second-line therapies. If this is the case, please update the model to include an option to reduce second-line treatment costs to account for patients who will not survive to reach second-line.

The EAG is correct that the model does not accurately capture treatment for these patients. In order to model this accurately we would need to know the proportion of patients in the metastatic trials whose first PFS event was a death rather than a progression. These data are not reported in KEYNOTE-189/407 or FLAURA and, given the amount to which correcting this could plausibly affect the ICER, we were

unable to prioritise examining the KEYNOTE trial databases. To our knowledge, these data have rarely been presented in NICE appraisals of metastatic cancer treatments but our recollection of TA939 (pembrolizumab for metastatic cervical cancer), which used a Markov model instead of a partitioned survival model meaning that these data could be inferred, was that the implied proportion of PFS events that were deaths was close to 10% in both arms. We therefore suggest reducing the proportion on active 2L treatment by 10%. This has a very small impact on the ICER because these treatments are inexpensive and used equally in both arms.

B32. Priority question. The EAG's clinical experts stated that given the average age of patients and the toxicity of cisplatin, carboplatin is preferred in clinical practice. This was also noted by the company's clinical advisors in the provided advisory board document in which it is stated that, "*A preference for carboplatin-based over cisplatin-based chemotherapy was indicated by all advisors*". Cisplatin is assumed to be part of the pembrolizumab and pemetrexed combination subsequent treatments. Therefore, as a scenario please assume that only carboplatin is provided as a platinum-based treatment in subsequent treatments.

Unfortunately we have not had time to provide this scenario. It is important to note, however, that both cisplatin and carboplatin are inexpensive treatments and the total cost per administration is very similar between the two. Because this suggested change would apply to both arms equally and because carboplatin is the slightly more expensive option, running this scenario would result in a very slight decrease in the ICER as subsequent treatments would become marginally more expensive.

B33. Priority question: In the submission, dosing schedules are presented in Table 54 for subsequent treatments.

a) **The dosing regimens for docetaxel and vinorelbine are missing from this table. Please provide this information.**

We have updated Table 54 from the CS to include both docetaxel and vinorelbine dosing regimens and list price per vial or pack as summarised in Table 26.

Table 26. Updated unit drug costs for treatments in the adjuvant, local-regional recurrence, and/or distant metastases settings

Regimen or component	Strength per vial or tablet (mg)	Dosing schedule	Source	List price per vial or pack (£)
Carboplatin	450	AUC 6 mg/ml/min IV Q3W, up to 4 cycles	As per Table 59 of CS	£14.69
Cisplatin	50	75 mg/m2 IV Q3W, up to 4 cycles (metastatic)	As per Table 59 of CS	£6.03
		100 mg/m2 IV Q4W (vinorelbine+cisplatin)	EMA, EPAR	
Docetaxel	160	75 mg/m2 IV Q3W	As per Table 59 of CS	£16.04
Osimertinib	80	80 mg orally once daily	As per Table 59 of CS	£5,385*
Paclitaxel	300	200 mg/m2 IV Q3W, up to 6 cycles	As per Table 59 of CS	£15.97
Pemetrexed	100	500 mg/m2 IV Q3W	As per Table 59 of CS	£125
Vinorelbine	50	25 mg/m2 IV QW	EMA, EPAR	£15.86

*MSD are do not know the PAS price of osimertinib so are arbitrarily assuming a 60% discount in all our analyses. This can be corrected by the EAG at a later date.

b) The sources of the dosing schedules presented in Table 54 have been generally attributed to the BNF and eMIT. However, with exception of osimertinib, the drugs listed have specialised dosing regimens specific to the cancer they are being used to treat and as such, the dosing schedules aren't presented in the BNF and eMIT. Please provide the specific sources used to inform the dosing schedule of each drug.

We would like to correct the BNF and eMIT sources are for the unit costs in Table 54. We have added the sources in Table 26 in our response to question B33a). The dosing for the metastatic regimens can be found in Table 59 of the CS.

c) **Please explain why the dosing schedules for the drugs presented in Table 54 are the same irrespective of setting (LR or DM), treatment line (first of second) or treatment combination (e.g. carboplatin + paclitaxel, pembrolizumab + carboplatin + [nab-] paclitaxel) considered.**

The dosing regimens applied in the LR health state and DM (1L and 2L) are dependent on the sources used in the model. As an example, the vinorelbine + cisplatin regimen from Table 26 shows the cisplatin dosing schedule is 100 mg/m2 IV Q4W as per the EPAR. In the 1L metastatic setting as summarised in Table 59 of the CS, cisplatin (as part of the Pembrolizumab + pemetrexed + platinum regimen) dosing is 75 mg/m2 IV Q3W, up to 4 cycles based on the KEYNOTE-189 publications. The rationale for why some of 1L and 2L DM treatment dosing schedules are the same (namely pemetrexed, carboplatin and cisplatin) is because these treatments are part of the pembrolizumab combination regimen and placebo arm from KEYNOTE-189. As mentioned in the CS, we assumed a proportion of patients will receive this pembrolizumab combination in 1L and in 2L patients would no longer receive any I/O combinations i.e. a proportion of patients will receive the placebo arm of KEYNOTE-189 (chemotherapy). Since the pembrolizumab and placebo arms use the same source for the KEYNOTE-189 publications, the dosing schedules were the same across both chemotherapy regimens.

Health care resource use

B34. Priority question: In section B.3.3.4 of the CS, the company explains that the mean number of episodes per patient with AE and mean duration of AE episode were based on all patients experiencing an AE irrespective of treatment arm in KEYNOTE-091 (Table 49). The EAG considers that given placebo patients are not on active treatment, mean number of episodes per patient with AE and mean duration of AE episode may differ compared with patients on pembrolizumab. Additionally, the percentage of AE episodes resulting in hospitalisation may differ between treatment arms.

a) **Please fill in the below table and explore this in a scenario.**

Unfortunately, the mean number of episodes per patient with AE, mean duration of episodes (weeks) and % of AE episodes resulting in hospitalisations split by the pembrolizumab and placebo arms could not be simultaneously included in the

economic analysis in the time available as this would require structural changes to the model. Nonetheless we explored AE mean number of episodes per patient, mean duration and % of AE episodes resulting in hospitalisation separately in the model from KEYNOTE-091. Pembrolizumab and placebo are explored in Table 27 and Table 28 respectively. As an extreme scenario when exploring pembrolizumab AEs, the AE risk (%) by adjuvant treatment arm in the placebo arm was set to 0% across all AEs and the mean number of episodes, mean duration of AEs (weeks) and % of AE episodes resulting in hospitalisations were derived from the pembrolizumab arm from the KEYNOTE-091 HECON summary report.[23] When exploring the AEs for the placebo arm, we included the AE risk % from pembrolizumab as indicated in Table 28.

The mean duration of AE per unique event were originally produced in days from the HECON summary report and updated in the 'Raw -AEs' sheet. The 'Safety' sheet of the model converts into weekly cycle lengths consistent with the economic analysis. In the pembrolizumab arm, this scenario gave an ICER of ******/QALY gained and in the placebo arm an ICER of ******/QALY. We expect the EAG's proposed changes to make very little difference to the basecase ICER. This is because the AE parameters that have the most impact on the ICER are % AE risk by treatment. When exploring the AEs in the pembrolizumab arm, the % AE risk in the 'inactive' arm i.e. placebo is set to 0%, this can be considered an extreme scenario as the differential is higher than if applying both treatments simultaneously, given the % AE risks between pembrolizumab and placebo are broadly similar as seen in Table 27 and Table 28. Secondly, we also expect this to make very little difference to the base case ICER as the updated AE costs (as explained in B41) lowers the total AE cost as summarised in Table 27 and Table 28 which are applied as a one-time cost in the first cycle of the model trace. In the first scenario, the total AE cost for pembrolizumab is £128.72 and for placebo £0 and in the second scenario, the total AE cost for placebo is £136.40 and pembrolizumab is £80.60.

b) Please provide the exact source of data used to inform the proportion of AEs resulting in hospitalisations (i.e. location in the CSR) as the EAG was unable to identify this data in the CSR.

With reference to B34a) we have provided a summary of the HECON summary report from KEYNOTE-091. The AE risk (%) by adjuvant treatment arm, mean number of episodes per patient with AE and mean duration of episodes (weeks) can be found in Table 1 of the HECON summary report.[23] The % of AE episodes resulting in hospitalisations by pembrolizumab and placebo arms can be found in Table 2.

Table 27. total cost of AEs(weeks) for pembrolizumab

AE type	Pembrolizumab				Placebo
	AE risk (%)	Mean number of episodes per patient with AE	Mean duration of AE per episode (weeks)	% of AE episodes resulting in hospitalisation	AE risk (%)
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of AEs	£128.72				£0

Table 28. total cost of AEs (weeks) for placebo

AE type	Placebo				Pembrolizumab
	AE risk (%)	Mean number of episodes per patient with AE	Mean duration of AE per episode (weeks)	% of AE episodes resulting in hospitalisation	AE risk (%)
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dyspnoea	******	******	******	******	******
Hypertension	******	******	******	******	******
Hyponatraemia	******	******	******	******	******
Pneumonia	******	******	******	******	******
Pneumonitis	******	******	******	******	******
Weight increased	******	******	******	******	******
Total cost of AEs	£136.40				£80.60

B35. Priority question. According to the EAG's clinical experts, patients on active treatment would receive a CT scan every six months for the first five years and an annual CT scan from thereafter. The EAG notes that in the company's clinical advisory board meeting document, it is also stated that, "*The disease-free state value for CT scans should be two per year*". Please clarify why the advice from the advisory board was not included in the base case and conduct a scenario exploring this increase in health care resource use.

This was an error. The company has updated its base case to include CT scans every 6 months for the first 5 years and yearly between years 5-7, although feedback from the advisory board 2022 was that patients would be discharged back to primary care after 5 DF years. This scenario increases the ICER by about £100.

B36. Priority question. EAG's clinical experts outlined that on transition to DM (applied as a one-off cost in the first cycle upon entering the DM health state) all patients should receive a chest radiography and that only 60% of patients would receive a PET-CT scan and 30% an MRI. Therefore, please conduct a scenario using these resource use proportions.

We adjusted these proportions in the Raw – HCRU sheet to reflect these proportions, which resulted in an ICER of [redacted]/QALY gained.

B37. Priority question. The EAG's clinical experts outlined that on transition to the LR health state, of those assumed to receive radiotherapy (RT), no patients would receive hyper fractionated RT as they would be RT naive and the split between patients receiving standard fractionated and CHART would be 95% and 5%, respectively. Additionally, on average 20 fractions of treatment would be delivered during standard fractionated RT. Therefore, please conduct a scenario using these updated proportions and values for subsequent radiotherapy.

Unfortunately, we were unable to find evidence in our advisory board notes specifically supporting an unweighted average. We have therefore updated the base case RT costs in line with the proportions suggested by the EAG's clinical advisors. The RT cost in the model represents the cost of both RT (20% of patients) and the radiotherapy component of CRT (30% of patients), which was costed as being 20

fractions as in NG122. It was the 20% RT that was divided equally between the three RT regimens. Removing the 30 fraction regimen and updating the weights so that 95% of RT patients get 20 fractions and 5% get CHART gives a weighted average RT cost of £4,517 instead of the previous £5,557). This slightly increases the ICER for pembrolizumab.

B38. Please explain why an average of CHART, hyperfractionated and standard fractionated costs were used to estimate the cost of RT.

Please see the answer to B37 above.

B39. Health state resource use was informed from TA823, in which it was assumed that patients in the LRR health state would only receive CT scans if receiving active treatment to detect disease progression and not those receiving no treatment or palliative care. The company applies the resource use of CT scans (4 per year) from TA823 to 42% of patients (Sheet "Raw-HCRU", cell O48). Please clarify why this has been applied to 42% of patients only and the data used to inform this.

This was an error and has been updated to 82% to reflect the proportion receiving active treatment (table 58 of the CS).

Adverse events costs

B40. The EAG notes that for those adverse events that are not assumed to require hospitalisation, the company applies a cost of "Clinical Oncology (Previously Radiotherapy) total outpatient attendance", regardless of adverse event type.

a) **Please clarify why this cost was used rather than the specific outpatient cost associated with each adverse event?**

We investigated the outpatient HRG codes associated with service code 800 from the NHS reference costs and noted this included non-admitted (face-to face and non-face-to-face) and multi-professional non-admitted (face-to face and non-face-to-face) for first visit and subsequent visits. As the model does not differentiate between first and subsequent visits for those who experience a given AE but do not require hospitalisation, we applied the same total outpatient attendance for each adverse event for computational simplicity.

b) Please provide a scenario in which the proportion of adverse events not requiring hospitalisation are costed using the outpatient cost associated with each specific adverse event type.

In the interest of time we instead, explored the cost per AE not resulting in hospitalisation using the weighted average of non-admitted (face-to face and non-face-to-face) and multi-professional non-admitted (face-to face and non-face-to-face) in the outpatient setting (service code 800) as summarised in Table 29. The weighted average calculation of £163.79 is very similar to the total outpatient attendance unit cost applied in the CS of £160.43

Table 29. Outpatient HRG codes for AEs not resulting in hospitalisations

Description	Number of attendances	Unit costs	Source
Non-Admitted Face-to-Face Attendance, Follow-up	703453	£164.19	NHS reference costs 2021/22 (HRG: WF01A-D)
Non-Admitted Face-to-Face Attendance, First	192818	£206.47	
Non-Admitted Non-Face-to-Face Attendance, Follow-up	454636	£132.90	
Non-Admitted Non-Face-to-Face Attendance, First	31847	£164.22	
Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	63852	£209.54	NHS reference costs 2021/22 (HRG: WF02A-D)
Multiprofessional Non-Admitted Face-to-Face Attendance, First	15171	£286.34	
Multiprofessional Non-Admitted Non-Face-to-Face Attendance, Follow-up	17116	£202.37	

Multiprofessional Non-Admitted Non-Face-to-Face Attendance, First	710	£278.17	
Weighted average	**£163.79**		**Calculation**

Using the above weighted average for adverse events not requiring hospitalisations did not alter the ICER, resulting in an ICER of [redacted]/QALY gained.

B41. The EAG found a number of discrepancies in the costs used for adverse events, based on the information provided by the company, described in the below table. Please clarify the exact HRG codes used to calculate the weighted averages from the NHS reference costs to explain these discrepancies. If the original values used were errors, please amend these in an updated model.

Grade 3-5 AEs	Company cost used	Source	EAG comment
Diarrhoea	£230	NHS Reference Cost 2021/22, FD10: Non-Malignant Gastrointestinal Tract Disorders - Regular Day or Night Admissions (weighted average)	Weighted average of codes of FD10JL:FD10M for regular day and night admissions is calculated as £222.40. Please clarify this discrepancy
Dyspnoea	£589	NHS Reference Cost 2021/22, DZ19: Other Respiratory Disorders - Regular Day or Night Admissions (weighted average)	Weighted average of codes of DZ19L:DZ19M for regular day and night admissions is calculated as £338.65. Please clarify this discrepancy
Hypertension	£193	NHS Reference Cost 2021/22, EB04Z: Hypertension - Regular Day or Night Admissions	Exact cost used should be £192.76
Pneumonia	£1,916	NHS Reference Costs 2021/2022 [DZ11T Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9]	Please clarify why the cost for 'Total HRGs' was used as opposed to Day or Night admissions for all other AEs?

Thanks for pointing out these inconsistencies. We reviewed the HRG codes that were chosen for the adverse event costs and on reflection, do not feel that there was a strong rationale for the specific codes and CC mixes chosen in the CS. In the absence of being able to make any concrete assumptions about what constitutes a "hospitalisation" we decided to make no assumptions and use all HRG codes. We have updated the model to include the weighted average for all HRG codes for all complications and comorbidities (CC) from NHS reference costs and provided further clarity in the description in the source column, please refer to Table 30.

Table 30. Updated AE costs used in the model

Grade 3-5 AEs	Cost per event resulting in hospitalisation (from CS)	Updated cost per event resulting in hospitalisation	Source
Diarrhoea	£230	£1,422.46	NHS Reference Cost 2021/22, FD10J-M: Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-11+ - Total HRGs (weighted average)
Dyspnoea	£589	£760.96	NHS Reference Cost 2021/22, DZ19L-N: Other Respiratory Disorders without Interventions, with CC Score 0-11+ Total HRGs (weighted average)
Hypertension	£193	£770.10	NHS Reference Cost 2021/22, EB04Z: Hypertension - Total HRG
Hyponatraemia	£238	£771.47	NHS Reference Cost 2021/22, WH13A-C: Abnormal Findings without Diagnosis - Total HRGs (weighted average)
Pneumonia	£1,916	£2,258.95	NHS Reference Costs 2021/2022 [DZ11R:V Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-14+ (weighted average)
Pneumonitis	£1,916	£2,258.95	Assume same cost as Pneumonia

Weight increased	£0	£0	Reference: CTCAE guidelines. Assume zero cost (investigation)

Other costs

B42. Priority question. The EAG's clinical experts advised that in the NHS, PD-L1 tests are routinely conducted upon diagnosis of NSCLC.

a) Please justify inclusion of PD-L1 test costs in the model.

When patients are diagnosed with early-stage NSCLC, the PD-L1 testing is currently determined based on the eligibility criteria for atezolizumab based on the NICE appraisal (TA823) i.e. the PD-L1 >50% subpopulation. As atezolizumab is currently recommended by NICE via the CDF, we have assumed PD-L1 testing is not routine in early-stage NSCLC (we note more and more centres in England are requesting PD-L1 testing to be conducted upfront). For the economic analysis, we conservatively assumed that patients who are diagnosed with early-stage NSCLC need PD-L1 testing to determine their eligibility for pembrolizumab i.e. PD-L1<50% TPS and so we included this cost in the pembrolizumab arm.

b) Please provide a scenario where the costs of PD-L1 tests are excluded.

Assuming no PD-L1 testing for patients in the pembrolizumab arm produces an ICER of ****** gained in the company's original base case model.

B43. Terminal care costs for cancer are available from the latest PSSRU Unit Costs of Health and Social Care 2022 Manual (Table 7.2.2). Please explore the PSSRU cancer end of life care cost in a scenario.

We have taken this to mean the final year of life from the 'cancer' diagnostic group from the combined hospital and social care setting, which has a cost £13,113 from Table 7.2.2 of the PSSRU Unit Costs of Health and Social Care 2022 Manual. No inflation was applied given the PSSRU source had the same cost year as this economic analysis. Applying this terminal care cost in the KEYNOTE-091 model to deaths from any state, produces an ICER of ****** gained.

Section C: Textual clarification and additional points

C1. In Table 51 of the CS, the estimated AE disutility is -0.116, but in the economic model (tab "Safety" cells G36:H36), this disutility is -0.016. Please clarify whether the CS or the model is correct and amend where relevant.

We would like to clarify that the total AE-related QALY decrement in the pembrolizumab arm is -0.0155 (-0.016 due to rounding), which is applied in the model trace sheet in cycle 0 and is updated in Table 31. The total AE-related QALY decrement in the placebo arm is also provided for completeness (-0.0158). The methodology for how this was calculated is detailed in B.3.4.4 of the CS but provided below for context. The total AE-related QALY decrement was calculated as a function of treatment specific AE risks, the mean duration of AEs per episode; the mean number of episodes per affected patient in KEYNOTE-091 (as summarised in Table 49 of the CS) and the estimated disutility associated with an active grade 3+ AE based on analyses of EQ-5D-3L data from the KEYNOTE-091 trial. The AE disutility of -0.116 included in Table 51 of the CS refers to the last component of this function i.e. disutility of an active grade 3+ AE from KEYNOTE-91. The methodology of how this was calculated is also provided in B.3.4.4 of the CS.

We would also like to correct the SE for the disutility for grade 3+ AEs as 0.038 instead of 0.033 as originally included in Table 51 of the CS. This has been updated in Table 31.

Table 31. Updated Estimated AE disutility (total QALYs) for grade 3+ AEs and Total AE-related QALY decrement

	Descriptive estimated decrement		Source
	Mean	**SE**	
Disutility for grade 3+ AEs	-0.116	0.038	KEYNOTE-091 (Jan 2023 data cut-off)
	Pembrolizumab	**Placebo**	**Source**
Total AE-related QALY decrement	-0.0155	-0.0158	Calculation

Abbreviations: AE adverse event; DF: disease free

C2. The ICER in Scenario 9 presented in Table 68 appears to have been rounded incorrectly. The value listed is £23,709 and should be £23,710. Please confirm which value is correct.

We can confirm the result for Scenario 9 i.e. applying the Weibull distribution for DF to the LR transition and log-normal distribution to the DF to DM transition to both pembrolizumab and placebo arms, the ICER is ****** gained.

C3. The EAG was unable to replicate the weighted average cost applied for PET-CT scans from the NHS Reference Costs using the information provided. Please clarify exactly which costs were used to calculate the value of £722.11.

We estimated the cost of PET-CT scans using a weighted average of the unit costs and the number of activities from PET-CT scan HRG codes RN01A, RN02A and RN03A, which were all derived from NHS reference costs 2021/22. We have provided further description for each HRG code, the associated unit costs and number of activities and weighted average cost in Table 32.

Table 32.Weighted average cost of PET-CT

HRG code and description	Number of activities	Unit cost (£)	Source
RN01A - Positron Emission Tomography with Computed Tomography (PET-CT) of One Area, 19 years and over	1,949	400	NHS reference costs(2021-22)[24]
RN02A - Positron Emission Tomography with Computed Tomography (PET-CT) of Two or Three Areas, 19 years and over	550	703	
RN03A - Positron Emission Tomography with Computed Tomography (PET-CT) of more than Three Areas, 19 years and over	3135	926	
Total cost of PET-CT scan	**£722**		**Calculation**

References

1. European Medicines Agency (EMA). EMEA/H/C/003820/II/0121. Keytruda European Public Assessment Report (EPAR). Available from: https://www.ema.europa.eu/documents/variation-report/keytruda-h-c-003820-ii-0121-epar-assessment-report-variation_en.pdf. . 2023.
2. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet. 2021;398(10308):1344-57.
3. MSD. Data on File. KEYNOTE-091 IA3 Statistical Report.
4. Zhang M, Li G, Wang Y, Wang Y, Zhao S, Haihong P, et al. PD-L1 expression in lung cancer and its correlation with driver mutations: a meta-analysis. Scientific Reports. 2017;7(1):10255.
5. Pawelczyk K, Piotrowska A, Ciesielska U, Jablonska K, Gletzel-Plucinska N, Grzegrzolka J, et al. Role of PD-L1 Expression in Non-Small Cell Lung Cancer and Their Prognostic Significance according to Clinicopathological Factors and Diagnostic Markers. Int J Mol Sci. 2019;20(4).
6. Royal College of Physicians. National Lung Cancer Audit. Spotlight report on molecular testing in advanced lung cancer, January 2020. 2020.
7. Skov BG, Rørvig SB, Jensen THL, Skov T. The prevalence of programmed death ligand-1 (PD-L1) expression in non-small cell lung cancer in an unselected, consecutive population. Modern Pathology. 2020;33(1):109-17.
8. Dietel M, Savelov N, Salanova R, Micke P, Bigras G, Hida T, et al. Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non-small-cell lung cancer: The global, multicenter EXPRESS study. Lung Cancer. 2019;134:174-9.
9. Lin G, Fan X, Zhu W, Huang C, Zhuang W, Xu H, et al. Prognostic significance of PD-L1 expression and tumor infiltrating lymphocyte in surgically resectable non-small cell lung cancer. Oncotarget. 2017;8(48):83986-94.
10. Wakelee H, Liberman M, Kato T, Tsuboi M, Lee SH, Gao S, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N Engl J Med. 2023;389(6):491-503.
11. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022;386(21):1973-85.
12. National Institute for Health and Care Excellence (NICE). Resource impact report: Atezolizumab monotherapy for untreated advanced non-small cell lung cancer (TA705). Available from: https://www.nice.org.uk/guidance/ta705/resources. [Access Date: 17 April 2024]. 2021.
13. Jessica B, Ayre G, Comins C, Dangoor A, Brooks H, Owadally W. 77 Toxicity and outcomes for patients with resected Non-Small cell lung cancer (NSCLC) who have received adjuvant chemotherapy in Bristol. Lung Cancer. 2024;190:107638.
14. Ugolini S, Granato F, Abdelghafar M, Moss A, Califano R, CoveSmith L, et al. 65 - A regional clinical audit of the provision of adjuvant systemic anti-cancer treatment following lung cancer resection in eligible patients across Greater Manchester to support national benchmarking. Lung Cancer. 2023;178:S28-S9.

15. Escriu C, Rathinam S, Kahangire D, Nagar S, Davis K, Jimenez M, et al. 39 - Patient characteristics and treatment patterns in resectable early-stage NSCLC: UK subgroup analysis of a global real-world study. Lung Cancer. 2023;178:S17.
16. Trevelyan G, Probyn B, Corcoran J, Howell T, Iyer A, Taylor L, et al. 131 Early stage lung cancer outcomes – a 10 year review of surgery and radiotherapy in patients with performance status 0-1 and Stage I and II NSCLC lung cancer. Lung Cancer. 2024;190:107692.
17. Felip E, editor Atezolizumab vs best supportive care in Stage II-IIIA NSCLC with high PD-L1 expression: sub-analysis from the pivotal Phase III IMpower010 study. European Lung Cancer Congress (ELCC); 2022.
18. Felip E, Altorki N, Zhou C, Vallieres E, Martinez-Marti A, Rittmeyer A, et al. Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial. Annals of Oncology. 2023;34(10):907-19.
19. Amdahl. Flexible parametric mixture and non-mixture cure models for time-to-event data. Available from: https://cran.r-project.org/web/packages/flexsurvcure/index.html. [Access Date: 25 April 2024] 2022.
20. Sonoda D, Matsuura Y, Ichinose J, Nakao M, Ninomiya H, Mun M, et al. Ultra-late recurrence of non-small cell lung cancer over 10 years after curative resection. Cancer Manag Res. 2019;11:6765-74.
21. Williams C, Lewsey JD, Briggs AH, Mackay DF. Cost-effectiveness Analysis in R Using a Multi-state Modeling Survival Analysis Framework: A Tutorial. Med Decis Making. 2017;37(4):340-52.
22. NHS England. National Cancer Drugs Fund list. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1.294.pdf. [Access Date: 28 February 2024].
23. MSD. Data On File. BARDS HECON: Safety Analyses - Summary report.
24. NHS England. NHS Reference Costs. 2021/22 National Cost Collection Data Publication. Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/. [Access Date: 29 February 2024].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Clarification questions

April 2024

File name	Version	Contains confidential information	Date
ID3907 pembrolizumab additional clarification questions 11042024 v2.0 [CON]	**2.0**	**Yes**	**11/04/2024**

[redacted]

Notes for company

Highlighting in the template

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

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

Additional clarification questions

PD-L1 expression

1. In Table 35 of the CS, data are provided on the baseline characteristics of participants of KEYNOTE-091, however no specific source references are provided. The EAG was unable to locate the reference/data-on-file for body surface area and weight.

    a. Please provide the missing source references for each of these tables, as the study CSR does not contain all of the data?

The baseline characteristics of the KEYNOTE-091 ITT population was based on Table 2 of the KEYNOTE-091 IA3 protocol HECON summary report, which MSD have uploaded on NICE documents. The glomerular filtration rate (GFR) (ml/min/1.73m^2) was based on the NICE TA181 submission as referenced in the CS[1].

    b. Please provide a version of Table 35 using only data from the PD-L1 TPS < 50% subpopulation of KEYNOTE-091.

We supplied the PD-L1 TPS <50% in our clarification response submitted on the 25th April (please see Table 14, question B1). We have removed the ITT population from the table and added further clarity on the source.

Table 1. Baseline characteristics from KEYNOTE-091 for PD-L1 <50% TPS subpopulation

Characteristic	PD-L1 <50%	Source
Starting age (years), mean	******	KEYNOTE-091 (Table 5 HECON summary report)
Percentage female (percentage)	******	
Body surface area (m^2), mean	******	
Body surface area (m^2), standard error	******	
Weight (kg), mean	******	
Weight (kg), standard error	******	
Glomerular filtration rate (GFR) (ml/min/1.73m^2)	75.0	NICE TA181[1].

Systematic literature review

2. The EAG notes that conference abstracts were primarily searched via Ovid using the Northern Light database, however the EAG was unable to identify any data on the quality of indexing and/or coverage of the Northern Light database. Please provide evidence that the Northern Light database appropriately indexes all conference abstracts from the American Society of Clinical Oncology, European Society for Medical Oncology and World Conference on Lung Cancer conferences.

The Northern Light database is a valid source for conference abstracts not published as journal supplements, with abstracts and posters from life sciences industry conferences being searchable within 3 weeks or less of the information posted on conference site.[2] To ensure the capture of all relevant conference proceedings, database searches of conference abstracts indexed in the Northern Light database (ASCO 2022-2023, ESMO 2022 and WCLC 2022-2023) were supplemented with hand searches. As described in the CS, ESMO 2023 was not indexed in the Northern Light database at the time of the systematic literature review so this conference was searched entirely by hand.

3. The EAG notes that the RoB-2 checklist was completed on the outcome level of disease-free survival (DFS), but that, i) no risk of bias assessment was presented for outcomes entering the model, e.g. OS, and ii) only a "traffic-light" coloured summary of the risk of bias domains were provided, rather than free-text justification of the risk of bias for individual RoB-2 items. Please:

    a. Provide a risk of bias assessment for KEYNOTE-091 for OS, EQ-5D, AEs and time on treatment.
    b. Provide free-text justifications for each item of the RoB-2 checklist, for DFS and any further assessments conducted.

Risk of bias assessment for each item of the RoB-2 checklist and for the outcomes listed above is provided in Table 3Table ***8***. Description of the RoB-2 domains is provided in Table 2.

Table 2. Cochrane risk of bias assessment tool

Domain	Question
Bias arising from the randomization process	
1.1	Was the allocation sequence random?
1.2	Was the allocation sequence concealed until participants were enrolled and assigned to interventions?
1.3	Did baseline differences between intervention groups suggest a problem with the randomization process?
Bias arising due to deviations from the intended interventions (effect of assignment to intervention)	
2.1	Were participants aware of their assigned intervention during the trial?
2.2	Were carers and people delivering the interventions ware of participants' assigned intervention during the trial?
2.3	If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?
2.4	If Y/PY to 2.3: Were these deviations likely to have affected the outcome?
2.5	If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?
2.6	Was an appropriate analysis used to estimate the effect of assignment of intervention?
2.7	If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?
Bias due to missing outcome data	
3.1	Were data for this outcome available for all, or nearly all, participants randomized?
3.2	If N/PN/NI to 3.1: Is there evidence that the results was not biased by missing outcome data?
3.3	If N/PN to 3.2: Could missingness in the outcome depend on its true value?
3.4	If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?
Bias in measurement of the outcome	
4.1	Was the method of measuring the outcome inappropriate?
4.2	Could measurement or ascertainment of the outcome have differed between intervention groups?
4.3	If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?
4.4	If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?
4.5	If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?
Bias in selection of the reported result	
5.1	Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?
5.2	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?
5.3	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?

Table 3. Cochrane risk of bias assessment of KEYNOTE-091, domain 1

Trial ID	Outcome	1.1	1.2	Support, 1.1&1.2	1.3	Support, 1.3	Judgment
KEYNOTE-091	AEs	Y	Y	Stratified randomization via IVRS	N	Comparable between arms	Low
	EQ-5D	Y	Y	Stratified randomization via IVRS	N	Comparable between arms	Low
	Time on treatment	Y	Y	Stratified randomization via IVRS	N	Comparable between arms	Low
	OS	Y	Y	Stratified randomization via IVRS	N	Comparable between arms	Low
	DFS	Y	Y	Stratified randomization via IVRS	N	Comparable between arms	Low

Abbreviations: AE, adverse events; DFS, disease-free survival; IVRS, interactive voice response system; N, no; OS, overall survival; Y, yes.

Table 4. Cochrane risk of bias assessment of KEYNOTE-091, domain 2 (part 1)

Trial ID	Outcome	2.1	2.2	Support, 2.1&2.2	2.3	Support, 2.3	2.4	Support, 2.4	Judgment
KEYNOTE-091	AEs	N	N	Triple-blinded	NA	--	NA	--	Low
	EQ-5D	N	N	Triple-blinded	NA	--	NA	--	Low
	Time on treatment	N	N	Triple-blinded	NA	--	NA	--	Low
	OS	N	N	Triple-blinded	NA	--	NA	--	Low
	DFS	N	N	Triple-blinded	NA	--	NA	--	Low

Abbreviations: AE, adverse events; DFS, disease-free survival; N, no; NA, not applicable; OS, overall survival.

Table 5. Cochrane risk of bias assessment of KEYNOTE-091, domain 2 (part 2)

Trial ID	Outcome	2.5	Support, 2.5	2.6	Support, 2.6	2.7	Support, 2.7	Judgment
KEYNOTE-091	AEs	NA	--	Y	Outcomes assessed in safety population (randomized patients who received ≥1 study treatment administration)	NA	--	Low
	EQ-5D	NA	--	Y	Outcome assessed in ITT population	NA	--	Low

Trial ID	Outcome	2.5	Support, 2.5	2.6	Support, 2.6	2.7	Support, 2.7	Judgment
	Time on treatment	NA	--	Y	Outcomes assessed in safety population (randomized patients who received ≥1 study treatment administration)	NA	--	Low
	OS	NA	--	Y	Outcome assessed in ITT population	NA	--	Low
	DFS	NA	--	Y	Outcome assessed in ITT population	NA	--	Low

Abbreviations: AE, adverse events; DFS, disease-free survival; ITT, intent-to-treat; NA, not applicable; OS, overall survival; Y, yes.

Table 6. Cochrane risk of bias assessment of KEYNOTE-091, domain 3

Trial ID	Outcome	3.1	Support, 3.1	3.2	Support, 3.2	3.3	3.4	Support, 3.3 & 3.4	Judgment
KEYNOTE-091	AEs	Y	Safety population included 99% of randomized patients	NA	--	NA	NA	--	Low
	EQ-5D	N	Majority of patients completed questionnaire at early timepoints, but not at later timepoints	N	No analyses performed to correct for bias	PN	NA	Completion rates were similar between treatment arms	Low
	Time on treatment	Y	Safety population included 99% of randomized patients	NA	--	NA	NA	--	Low
	OS	Y	Outcome data available for all randomized participants	NA	--	NA	NA	--	Low
	DFS	Y	Outcome data available for all randomized participants	NA	--	NA	NA	--	Low

Abbreviations: AE, adverse events; DFS, disease-free survival; N, no; NA, not applicable; OS, overall survival; PN, probably no; Y, yes.

Table 7. Cochrane risk of bias assessment of KEYNOTE-091, domain 4

Trial ID	Outcome	4.1	Support, 4.1	4.2	Support, 4.2	4.3	Support, 4.3	4.4	4.5	Support, 4.4 & 4.5	Judgment
KEYNOTE-091	AEs	PN	Assessed by investigators using validated instruments	PN	Measured similarly between arms	N	Blinded investigator assessment	NA	NA	--	Low
	EQ-5D	PN	Collected by the investigator and measured using validated instruments	PN	Measured similarly between arms	N	Blinded investigator assessment	NA	NA	--	Low
	Time on treatment	PN	Treatment was prepared, dosed, and administered by a pharmacist	PN	Measured similarly between arms	N	Blinded investigator assessment	NA	NA	--	Low
	OS	PN	Recorded by the investigator	PN	Measured similarly between arms	N	Blinded investigator assessment	NA	NA	--	Low
	DFS	PN	Assessed by investigators using validated instruments	PN	Measured similarly between arms	N	Blinded investigator assessment	NA	NA	--	Low

Abbreviations: AE, adverse events; DFS, disease-free survival; N, no; NA, not applicable; OS, overall survival; PN, probably no; Y, yes.

Table 8. Cochrane risk of bias assessment of KEYNOTE-091, domain 5

Trial ID	Outcome	5.1	Support, 5.1	5.2	Support, 5.2	5.3	Support, 5.3	Judgment
KEYNOTE-091	AEs	Y	Analyzed in accordance with pre-specified analysis plan	N	Based on the trial protocol	PN	Based on the analysis plan	Low
	EQ-5D	Y	Analyzed in accordance with pre-specified analysis plan	N	Based on the trial protocol	PN	Based on the analysis plan	Low

Trial ID	Outcome	5.1	Support, 5.1	5.2	Support, 5.2	5.3	Support, 5.3	Judgment
	Time on treatment	Y	Analyzed in accordance with pre-specified analysis plan	N	Based on the trial protocol	PN	Based on the analysis plan	Low
	OS	Y	Analyzed in accordance with pre-specified analysis plan	N	Based on the trial protocol	PN	Based on the analysis plan	Low
	DFS	Y	Analyzed in accordance with pre-specified analysis plan	N	Based on the trial protocol	PN	Based on the analysis plan	Low

Abbreviations: AE, adverse events; DFS, disease-free survival; N, no; OS, overall survival; PN, probably no; Y, yes.

Economic model

4. **Priority: For first line metastatic subsequent therapies, Table 59 of the CS reports that 59.6% of patients will receive paclitaxel and 40.4% receive nab-paclitaxel when used as part of the carboplatin + (nab-)paclitaxel regime. When used as part of the pembrolizumab + carboplatin + (nab-)paclitaxel regime, Table 59 reports 60.8% of patients will receive paclitaxel and 39.2% receive nab-paclitaxel. However, in the economic model in Sheet "Drug & Admins Costs", 100% of patients are assumed to receive paclitaxel, with no patients reported to receive nab-paclitaxel. Please clarify the correct proportions that should be used in the model and amend either Table 59 or the economic model accordingly.**

We would like to confirm the proportion receiving paclitaxel is correct in the economic model and apologies for any confusion in Table 59. The advice we received from our clinical advisers is that that nab-paclitaxel is not in use in the UK. Therefore 100% of these patients would receive paclitaxel.

5. Please provide all references used to obtain survival data by treatment in the first-line metastatic NSCLC setting (sources referenced in the model worksheet “Raw - 1L DM Efficacy” in cells J10:N71). If any of the sources cite the wrong reference, please update them in future iterations of the model.

We can confirm the sources in J10:N71 are correct. The KEYNOTE-407 (pembrolizumab + carboplatin + paclitaxel) and KEYNOTE-189 (pembrolizumab + pemetrexed + platinum) sources used to estimate the weekly exponential rates for death and PFS were updated in the model to include the Novello et al. (2023) and Garassino et al. (2023) papers respectively. These were the same publications shared with the EAG on the 18th March 2024.

References

1. National Institute for Health and Care Excellence (NICE). TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta181. 2009.
2. Wolters Kluwer. Northern Light Life Sciences Conference Abstracts. Available from: https://www.wolterskluwer.com/en/solutions/ovid/northern-light-life-sciences-conference-abstracts-13207. [Access date: 15 May 2024].

Table 1. Updated scenario analyses without osimertinib discount

Scenario	Incremental costs (£)	Incremental QALYs	Incremental LYs	ICER vs. comparator (£/QALY)
Base-Case	[redacted]	0.93	1.10	[redacted]
Cure point 5 years	[redacted]	0.93	1.10	[redacted]
Cure point 5-10 years	[redacted]	0.91	1.08	[redacted]
Calibration cap 6-8 years	[redacted]	0.96	1.15	[redacted]
Calibration removed entirely	[redacted]	0.71	0.80	[redacted]
Calibration removed, SEER adjustment added	[redacted]	0.62	0.67	[redacted]
Calibration without SEER-Medicare adjustment	[redacted]	0.92	1.09	[redacted]
Pembrolizumab given Q6W	[redacted]	0.93	1.10	[redacted]
Exponential/log-normal DFS curves	[redacted]	0.93	1.10	[redacted]
Weibull/log-normal DFS curves	[redacted]	0.88	1.05	[redacted]
Log-logistic/log-normal DFS curves	[redacted]	0.92	1.09	[redacted]
Gamma/log-normal DFS curves	[redacted]	0.90	1.07	[redacted]
Approach #2 Gompertz/Weibull DFS curves	[redacted]	0.99	1.17	[redacted]
Approach #3 Exponential/Exponential DFS Curves	[redacted]	1.19	1.41	[redacted]
20% of DM patients on no active treatment	[redacted]	0.92	1.09	[redacted]
DF utilities including g1-2 Aes	[redacted]	0.87	1.10	[redacted]
G3+ AE disutilities excluded	[redacted]	0.93	1.10	[redacted]
100% cure assumption	[redacted]	0.93	1.10	[redacted]
RDI included with full KM	[redacted]	0.93	1.10	[redacted]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

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.

NICE National Institute for Health and Care Excellence

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	**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; £480 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) - Novocure (£30,000 for 1 year funding of GLCC project) - Roche (£30,000 for 1 year funding of GLCC project; £525 Speaker Fee, Lung Cancer Conference) - Regeneron (£30,000 for 1 year funding of GLCC project) - Merck (£30,000 for 1 year funding of GLCC project)

companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	- AstraZeneca (£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	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.

to include in your submission?	

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	For patents with early stage lung cancer, who have a surgical resection of the tumour, with curative intent, the 5 year survival rates are reported to be up to 50%, with relapses in distant sites accounting for most failures. Relapse after surgery means that further potentially curative therapy is unlikely. Patients and their carers have continual anxiety that the lung cancer will come back. Symptoms of recurrent disease, such as breathlessness, cough and weight loss are often 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?	Historically, standard care for patients with resectable nsclc has been surgery. Sometimes, with the addition of chemotherapy after surgery (adjuvant) or chemoradiation before surgery (neoadjuvant). In March 2023, NICE approved Nivolumab (a different immunotherapy drug), with chemotherapy, for the neoadjuvant treatment of resectable nsclc (NICE TA876). There is current considerable interest in the use of immunotherapy in the adjuvant and neoadjuvant settings, with clinical trials, using a number of different agents.
8. Is there an unmet need for patients with this condition?	Yes. There is a need to explore additional therapies in improving outcomes and reducing recurrence in this patient group.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We note the results from the KEYNOTE-091 trial, which showed substantially improved disease free survival in patients in the pembrolizumab arm. Adverse events were as expected, based on known toxicity profiles for the therapy. Patient and carers would want the best outcome of systemic therapy. We are not aware of any direct comparisons, with other immunotherapies, in this indication.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The side effects associated with the therapy.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	
14. Under current clinical practice do people have neo-adjuvant treatment, followed by surgery and then adjuvant treatment? If so, what treatments are used as neo-adjuvant and adjuvant therapies?	
14b. If the answer to Q14 is no, what do most people currently have as treatments around (before and/or after) their surgery for locally advanced NSCLC?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• Adjuvant treatment is shown to be of benefit in the management of patients with early stage non small cell lung cancer • There is a need to develop therapy options to reduce the risk of recurrence after lung cancer surgery.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

NHS organisation submission

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and Social Care and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Social Care and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name	[redacted] / [redacted]
Name of your organisation	British Thoracic Oncology Group and on behalf of NCRI/RCP
Please indicate your position in the organisation	• [redacted] is a consultant medical oncologist at the Royal Marsden Hospital with a large NHS lung cancer practice. • [redacted] is a active member of BTOG. • [redacted] was and is [redacted] for the Keynote 091 (PEARLS trial) which started as an academic EORTC/ETOP trial but later funded and sponsored by Merck/MSD.
Do you have any links with, or funding from, the tobacco industry? Please declare any direct or indirect links to, and receipt of funding from the tobacco industry	no

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?	Currently patients with NSCLC stage IB- IIIA who are fit for surgery, proceed to surgery and if a complete resection (R0) is achieved and patient recovers to performance status (PS) 0,1, their pathology is discussed at an multidisciplinary meeting (MDM). The results of EGFR and PDL1 are also now done/requested and made available. Irrespective of the results of EGFR or PDL1, if the tumour is greater than 4cm with no nodes or the tumour is any size with lymph node N1 or N2 involved, then patients are offered chemotherapy for 4 cycles providing they are agreeable and have appropriate renal function etc (chemotherapy administration criteria). In addition: 1. If patients have tumour over 3cm (stage 1b-IIIa) and EGFR is positive for the 2 common sensitising mutations (Exon 19 and Exon 21 (L858), patients are offered 3 years of adjuvant Osimertinib as in the ADAURA trial.

Is there significant geographical variation in current practice?	2. If patients have stage II-IIIa disease (>5cms) and PDL1 is >50% (by any antibody used in the lab), patients are offered I year of adjuvant atezolizumab as in the IMPOWER 010 trial. There should be no geographic variation.
Are there differences in opinion between professionals as to what current practice should be?	There is still discussion on the use or need for chemotherapy in patients with EGFR mutations – in MVA for disease free survival (DFS) and now overall survival (OS) in the ADAURA trial, having chemotherapy did not come out as a statistical prognostic factor. The trial did not address, and would not have been powered for a small difference.
What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?	The current technology appraisal is for the use of pembrolizumab (an immunotherapy) in all patients with resected NSCLC regardless of the PDL1 rate of expression, for all tumours with lymph removed at surgery and found to be histologically involved (nodes positive) or if a tumour is greater than 4cm if nodes negative, who have completed adjuvant chemotherapy. Atezolizumab is currently only indicated for patients with PDL1 expression >50%, node positive tumours, or tumours greater than 5cm if lymph node negative. This is an add on therapy to standard chemotherapy, as PDL1 >50% can already receive adjuvant atezolizumab. This technology extends the use of adjuvant immunotherapy beyond the indications for adjuvant atezolizumab. In the Keynote 091 (PEARLS) trial, all subgroups benefitted, including patients with tumours 4-5cm and >5cms and patients with all PDL1 expression i.e. including PDL1 negative and 1-49%. Adjuvant pembrolizumab will improve outcome for more patients with resected lung cancer, over current standards of care. Using this treatment (pembrolizumab) for patients >50% PDL1 as an alternative to atezolizumab, will give patients the option of a treatment that is given less frequently – every 6 weeks rather than every 3-4 weeks.

	These new adjuvant immunotherapy technologies prolong DFS (recurrence – the second most devastating event in a lung cancer patients' life, the first being initial diagnosis) – which in general and in the past, run in parallel to OS. In advanced disease we now have 20% of patients with stage IV disease alive and well at 5 yrs. We are also expecting a lung term survival benefit for adjuvant immunotherapy. The advantages of pembrolizumab over atezolizumab are that the DFS benefits extend over a further cohort of patients not approved for atezolizumab (i.e small tumours 4-5cm, all PDL1 expression) and with an easier schedule of administration.

To what extent and in which population(s) is the technology being used in your local health economy?	Currrently adjuvant pembrolizumab is not being used as adjuvant therapy in the NHS – but I imaging it won't be long until it is used in the private sector. Pembrolizumab is widely used in patients with advanced stage IV lung cancer.
Is there variation in how it is being used in your local health economy?	We are following Nice guidance on the use of atezolizumab. No variation
Is it always used within its licensed indications? If not, under what circumstances does this occur?	Yes, currently always used within licence.
What is the impact of the current use of the technology on resources?	The resource impact is manpower to see patients every month/6 weeks for a year, to do extra bloods and to hospitalise and treat if toxicities occur (drug costs not discussed). Patients also need 3 monthly bloods during the second year after treatment for delayed immune toxicities.
What is the outcome of any evaluations or audits of the use of the technology?	We have done an audit on the use of 3 monthly blood tests after one year of adjuvant durvalumab when given after chemotherapy and radiotherapy. The results have been submitted for presentation at the BTOG 2024 meeting, and do suggest this is an important safety activity that should be continued.
What is your opinion on the appropriate use of the technology?	The use of adjuvant immunotherapy as in atezolizumab is going well; very well taken up by patients and toxicity very manageable with atezolizumab – my observation being that it is less toxic than when used in the advanced setting. I have had no patient refuse the treatment and no major toxicities. I expect to see more patients receiving adjuvant pembrolizumab as in this technology, especially given the easier schedule of 6 weekly treatment.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?	If pembrolizumab is funded and approved by NICE and NHS, the indications would thus mean an extended cohort of patients will be eligible – eligibility will include all patients without an EGFR mutation, with ANY PDL1 expression and with ANY completely resected stage Ib-IIIa – down to tumours as small as 4cms even if lymph nodes are negative. Patients would be offered chemotherapy, as the group who did not received chemotherapy in the KN091 trial did not appear to get benefit from pembrolizumab. In addition from the KN091 data, even if a patient received only 1-2 courses of adjuvant chemotherapy, rather than 3-4 courses, the adjuvant benefit was still there and hazard ratios for benefit were similar. As pembrolizumab can be given 6 weekly this will be an advantage over atezolizumab (3-4 weekly) but clinicians may still want access to atezolizumab for the >50% PDL1 as this was the group that benefited from atezolizumab, has longer followup, and is the group with recently presented OS data which was positive.
In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?	The technology (pembrolizumab for patients after surgery), 9 injections (6 weekly) iv, over one year, should be restricted to specialist cancer hospitals or supervised satellite sites where the expertise in the management of toxicity is available. There is a requirement for additional resources as all units around the country are seeing increased and long courses of immunotherapy across all tumour types. In Australia and now in Manchester they have

	developed a mobile home delivery of the iv immunotherapy as a more cost-effective option than hospital delivery (personal communication with Prof Paul Mitchel, health service representation in Melbourne). In the UK a focused training of specialist chemotherapy nurses, CNSs, PAs, ANP or AMPs, or pharmacists could be formalised, to run telephone clinics. Many on these health care professionals are also certified prescribers. This is running in some centres eg. Maidstone, but nationally could be taken up and skill sets levelled up. There are UK trials in the advanced setting (e.g. REFINE lung) looking at scheduling using 6 weekly pembrolizumab as a baseline standard of care.
Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).	The budget impact is the cost of the drugs. The impact on the NHS service has been addressed in the above boxes – consultations 9/yr, iv administration 9/year, pharmacy preparation 9/yr – are all extra episodes. In those patients receiving atezo (>50% PDL1), there will be a saving on the current planned 13 episodes, being reduced to 9 episodes per patient in a year. There will be no extra scans required above current scanning practice during year 1 after surgery. There will be 4 extra bloods tests (3 monthly) required year 2 after surgery, which will included testing thyroid function tests.

	The improvement in DFS will keep more patients active and able to work, and less in a disabled state of health from relapsed disease and therefore a benefit to society and NHS resources.
Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?	Difficult question but of course everything has spin of effects – all ill health is bad and not equal. We are not Oregon and we have not listed health needs as a funding priority in the NHS. But patients with lung cancer are in general socially deprived have given to the economy through a life time of smoking taxation and manual labour and are a big symptomatic burden on the NHS in the later part of their lives – many are diabetic and have comorbidities. This is a simple technology deliverable within current NHS resources. With some imaginative planning that is currently also needed and being developed, for the delivery of immunotherapy across the country for most tumour types increasingly, in both advanced disease and more recently in other common tumours (e.g adjuvant breast cancer), we should be able to absorb this technology.
Would there be any need for education and training of NHS staff?	No need for more education or training on the technology, but more training to develop a larger workforce of specialist nurses, chemotherapy nurses, and pharmacists to run clinics and deliver this service – currently being delivered in most centres by oncology special registrars and consultants. Contact to a central hotline/team leaders could be a safety resource for practitioners in more isolated areas or where oncology consultant input is not readily available due to our current workforce problems.

Equality

Please let us know if you think that this appraisal: **Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licenced** **Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology** **Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.**	NO NO People with disability were in general not included in the trial if it was felt that they were not performance status 0 or 1 or who could not give consent. The potential toxicities and their management (e.g. grade 3-4 diarrhoea) and the consent to this toxicity is something we do address in the advanced setting on a daily basis. Thus we will adapt this technology using the same principles of delivering evidence based and safe treatment to individuals after a holistic medical assessment of the risk and potential benefits.
Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.	There is no new evidence outside the reported clinical trials (Keynote 091/PEARLS).

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Other issues

Please include here any other issues you would like the appraisal committee to consider when appraising this technology	The data speaks for itself.

Your privacy

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

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

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.

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 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Royal College of Pathologists
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 A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation – a charity.
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.**	No
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 help to reduce the risk of recurrence following surgery in patients with potentially curable non-small cell lung cancer
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.)	As a pathologist, I do not have the expertise to answer this question.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Non-small cell lung cancer (especially in the UK) has a dismal prognosis. Most cases present late and are incurable. Gains in survival will likely come from either early detection or a higher rate of cure in the few patients suitable for surgery. It is therefore essential that this small group of potentially curable patients are given the best chance possible of cure.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	These patients usually undergo surgery, and may then receive adjuvant chemotherapy.
9a. Are any clinical guidelines used in the treatment of the	As a pathologist, I do not have the expertise to answer this question.

condition, and if so, which?	
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.)	As a pathologist, I do not have the expertise to answer this question.
9c. What impact would the technology have on the current pathway of care?	From a pathology point of view, there is unlikely to be any impact. Assuming that PD-L1 testing is not required to determine patient eligibility for this technology, impact will be zero. Even if PD-L1 testing were required, the impact would be minimal. The vast majority of UK centres already undertake PD-L1 testing at diagnosis of all non-small cell lung cancers; therefore, the vast majority of patients undergoing surgery will already have a PD-L1 score available when they undergo surgery, and this technology will not introduce any additional testing requirement.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As a pathologist, I do not have the expertise to answer this question.
10a. How does healthcare resource use differ between the technology and current care?	See above. From a pathology perspective, resource implications will be nothing if PD-L1 testing is not required, and will be minimal (compared to the current situation) if it is required.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	As a pathologist, I do not have the expertise to answer this question.

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	See above.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	As a pathologist, I do not have the expertise to answer this question.
11a. Do you expect the technology to increase length of life more than current care?	As a pathologist, I do not have the expertise to answer this question.
11b. Do you expect the technology to increase health-related quality of life more than current care?	As a pathologist, I do not have the expertise to answer this question.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As a pathologist, I do not have the expertise to answer this question.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare	See above.

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As a pathologist, I do not have the expertise to answer this question.
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?	As a pathologist, I do not have the expertise to answer this question.
16. Do you consider the technology to be innovative in its potential to make a significant and	As a pathologist, I do not have the expertise to answer this question.

substantial impact on health-related benefits and how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	As a pathologist, I do not have the expertise to answer this question.
16b. Does the use of the technology address any particular unmet need of the patient population?	As a pathologist, I do not have the expertise to answer this question.
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?	As a pathologist, I do not have the expertise to answer this question.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	As a pathologist, I do not have the expertise to answer this question.
18a. If not, how could the results be extrapolated to the UK setting?	As a pathologist, I do not have the expertise to answer this question.

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	As a pathologist, I do not have the expertise to answer this question.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	As a pathologist, I do not have the expertise to answer this question.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	As a pathologist, I do not have the expertise to answer this question.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	As a pathologist, I do not have the expertise to answer this question.
20. How do data on real-world experience compare with the trial data?	As a pathologist, I do not have the expertise to answer this question.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not to my knowledge
21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• This technology has the promise of improving outcomes for the small proportion of patients with non-small cell lung cancer who are potentially curable, and therefore may go some way towards improving outcomes in this poor-survival disease • Assuming that PD-L1 testing is not required, this will not impact on pathology services • Even if PD-L1 testing is required, the impact on pathology services will be minimal since the vast majority of patients with non-small cell lung cancer in the UK will have a PD-L1 score by the time of their surgery • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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

Please select YES if you would like to receive information about other NICE topics - NO

For more information about how we process your personal data please see our privacy notice.

BMJ TAG

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135657.

Title:	Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Melina Vasileiou, Clinical Evidence Analyst, BMJ-TAG, London Isaac Mackenzie, Health Economist, BMJ-TAG, London Ben Farrar, Senior Clinical Evidence Analyst, BMJ-TAG, London Kate Ennis, Senior Health Economist, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	23/05/2024
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135657.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Dr Pooja Jain (Consultant Clinical Oncologist, Leeds Cancer Centre, St James' University Hospital, Leeds Teaching Hospitals Trust) and Dr Zacharias Tasigiannopoulos (Consultant Clinical Oncologist, Norfolk & Norwich University Hospitals) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report. The EAG would also like to thank Dr Dionysis Papadatos-Pastos (Consultant Medical Oncologist, Lung Cancer Unit, University College London Hospitals and The Princess Alexandra Hospital) for providing feedback on the clinical sections of the report
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Vasileiou M, Mackenzie I, Farrar B, Ennis K. Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer: A Single Technology Appraisal. BMJ Technology Assessment Group, 2024

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Melina Vasileiou	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Ben Farrar	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and assisted with drafting the clinical results sections
Isaac Mackenzie	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Kate Ennis	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AEs	Adverse events
AESIs	Adverse events of special interest
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
APaT	All participants-as-treated population
AUC	Area under the curve
BIC	Bayesian information criterion
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CE	Conformité Européenne
CHMP	Committee for Medicinal Products for Human Use
CDF	Cancer Drugs Fund
CHART	Continuous Hyperfractionated Accelerated Radiotherapy
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPI	Consumer price index
CQ	Clarification question
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
DF	Disease free
DFS	Disease free survival
dL	Decilitre
DM	Distant metastases
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	Euroqol 5 dimensions
EU	European Union
FAS	Full analysis set

GB	Great Britain
GFR	Glomerular filtration rate
GI	Gastrointestinal
GP	General practitioner
HCRU	Health care resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUVs	Health state utility values
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
I/O	Immunotherapy
IPD	Individual patient data
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IU	International Units
IUCC	International Union Against Cancer
IV	Intravenous
kg	Kilogram
KM	Kaplan-Meier
LTFU	Long term follow-up
LR	Loco-regional
LRR	Local regional recurrence
MA	Marketing authorisation
MAIC	Matching-adjusted indirect comparison
MeSH	Medical subject headings
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed-effect model repeated-measure
MRI	Magnetic resonance imaging
MSD	Mark Sharp & Dohme
MSE	Mean squared errors
NA	Not applicable
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non- small cell lung cancer
ONS	Office of National Statistics

OR	Odds ratio
OS	Overall survival
OWSA	One way sensitivity analysis
PAS	Patient access scheme
PD-L1	Programmed death-ligand 1
PET-CT	Positron emission tomography–computed tomography
PFS	Progression free survival
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
Q3W	Every three weeks
Q6W	Every six weeks
QALY	Quality Adjusted Life Year
RDI	Relative dose intensity
RoB	Risk-of-bias
QoL	Quality of life
RCRD	Rapid Cancer Registration Dataset
RCT	Randomised controlled trial
SAEs	Serious adverse events
SCLC	Small cell lung cancer
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SOC	Standard of care
STA	Single technology appraisal
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TNM	Tumour-Node-Metastasis
ToT	Time on treatment
TPS	Tumour proportion score
TSD	Technical support document
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the External 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. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues contained within the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 presents a summary of the EAG's key issues on the evidence submitted on the clinical and cost effectiveness of pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer in PD-L1 TPS <50% patients who have received prior adjuvant chemotherapy.

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	The population of interest is a *post-hoc* subpopulation of a subgroup from the overall KEYNOTE-091 trial population	Sections 2.2.1, 2.3.1, 3.2
2	The baseline age from the trial, used in the model, is too low compared to the target population in clinical practice	Sections 2.3.1, 3.2 4.2.2.1
3	Better fitting DFS curves are available and should be used	Section 4.2.5.1.5
4	There is significant uncertainty in the trajectory of patient's post-recurrence due to limitations of the model structure and lack of available trial data	Sections 4.2.5.1.5, 4.2.5.3.2
5	The company's clinical experts recommended calibration should be limited to 5 years	Section 4.2.5.3.2
6	I/O ineligible patients with distant metastases in the pembrolizumab arm have better efficacy than I/O eligible patients in placebo	Section 4.2.5.3.2
7	Utility value for DF used by company, excluding grade 1/2 adverse events, is higher than general population	Section 4.2.6.4

Abbreviations: DF, disease free; DFS, disease free survival; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; I/O, immunotherapy; QALY, quality-adjusted life-year.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are as follows:

Table 2. Key differences between the company's preferred assumptions and the EAG's preferred assumptions

Assumption	Company preference	EAG preference
Baseline patient characteristics used in the model	Company preference is for the ITT population from the trial	EAG preference is for target population (PD-L1 <50%) from the trial where possible aside from baseline age which is taken from UK registry data.
Dosing frequency for pembrolizumab	Company preference is for Q3W for both adjuvant and metastatic pembrolizumab treatment. They provide a scenario using Q6W for adjuvant pembrolizumab and Q3W for metastatic.	EAG preference is for Q3 dosing to make up 25% of administrations and Q6W to make up 75% for both adjuvant and metastatic pembrolizumab.
Parametric curves used to model disease free survival	Company preference is for same curve used to model DF to LR and DF to DM for both pembrolizumab and placebo (all log-normal).	EAG preference is for different curves to account for potential treatment waning and better fit the available data. Pembrolizumab uses exponential/log-normal for transition to LR/DM and placebo uses generalised gamma/ gompertz.
When should the calibration be applied and to which patients	Company assumes calibration gradually reduced between years 5 and 7 along with treatment effect.	EAG assumes calibration is stopped at 5 years exactly.
Disease free utility value	Use utility value derived from KEYNOTE-091 which excludes all adverse events, including grade 1 and 2.	EAG preference is to use the utility value which includes grade 1/2 adverse events as the value used by the company is higher than the general population.

Abbreviations: DF, disease free; DFS, disease free survival; DM, distant metastases; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; I/O, immunotherapy; ITT, intention to treat; LR, local recurrence; PD-L1, Programmed death-ligand 1;

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.

Overall, the technology is modelled to affect QALYs by:

- Decreasing patients rate of transition from disease-free to health states with poorer quality of life: local recurrence, distant metastatic recurrence, and death, (increasing their disease-free survival);
- Decreasing rate of transition from local recurrence to distant metastatic recurrence and death;
- Decreasing the mortality of patients who experience a distant metastatic recurrence;
- Increasing rates of adverse events.

Overall, the technology is modelled to affect costs by:

- Decreasing patients rate of transition from disease-free to health states with different healthcare costs: local recurrence, distant metastatic recurrence, and death, (increasing their disease-free survival);
- Decreasing rate of transition to from local recurrence to distant metastatic recurrence and death;
- Decreasing the mortality of patients who experience a distant metastatic recurrence;
- Decreasing mortality rate, meaning end of life costs are accrued later in patients' life though patients cease to incur costs;
- Increasing rates of adverse events/hospitalisations due to adverse events.
- Increasing treatment costs for the first year;
- Different makeup of subsequent treatments due to I/O ineligibility in some adjuvant pembrolizumab patients.

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

- Estimation of disease-free survival curves;
- Cost of intervention;
- Cost/makeup of subsequent treatments.

1.3 The clinical effectiveness evidence: summary of the EAG's key issues

Table 3. Issue 1: The clinical evidence supporting the company submission relies on a *post-hoc* subgroup of the KEYNOTE-091 trial.

	Sections 2.2.1, 2.3.1, 3.2

Description of issue and why the EAG has identified it as important	The company positions pembrolizumab as an adjuvant therapy for patients with non-small cell lung cancer following complete resection and adjuvant chemotherapy, and with PD-L1 TPS <50%. This is a narrower population than specified in the marketing authorisation for pembrolizumab in this indication and follows the unexpected clinical finding of a numerically greater observed DFS and OS benefit of pembrolizumab in the PD-L1 TPS <50% subpopulation compared to the PD-L1 TPS ≥50% subpopulation of the KEYNOTE-091 trial. The EAG notes that the company has not presented sufficient evidence to support its assertion that the clinical findings are due to an ''overperforming'' control arm in the ≥50% subpopulation, as stated in the CS. The EAG notes that although the PD-L1 TPS 0% and 1-49% were prespecified subgroups and stratification factors in the KEYNOTE-091 trial, the target population for this appraisal was not a prespecified subgroup in the KEYNOTE-091 trial. The EAG considers the focus on this *post-hoc* subgroup to be at risk of overestimating the treatment effect of pembrolizumab in the PD-L1 TPS <50% subpopulation as the possibility of the company's choice to seek approval in this subgroup being data-driven cannot be ruled out. Nevertheless, given that the company positions pembrolizumab within the subgroup of patients with PD-L1 TPS <50% in the current CS, the EAG recognises that the *post-hoc* analysis of the PD-L1 TPS <50% subpopulation of the KEYNOTE-091 trial provides data that are directly applicable to the population addressed in the company's decision problem. In addition, the EAG notes that, as a result of focusing on a smaller subpopulation of the original sample required for the study to have sufficient power, results for the PD-L1 TPS <50% subpopulation are at risk of Type I error and so could be due to chance.
What alternative approach has the EAG suggested?	n/a; the EAG consider the company's approach to focus on the *post-hoc* subgroup of the KEYNOTE-091 trial appropriate as it provides the most relevant data to the company's decision problem but considers it to be at risk of bias and Type I error.
What is the expected effect on the cost-effectiveness estimates?	n/a
What additional evidence or analyses might help to resolve this key issue?	n/a

Abbreviations: CS, company submission; DFS, disease-free survival; EAG, External Assessment Group; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; TPS, tumour proportion score

Table 4. Issue 2: Younger age of participants in KEYNOTE-091 compared to patients in clinical practice in England.

Report section	Sections 2.3.1, 3.2, 4.2.2.1
Description of issue and why the EAG has identified it as important	The EAG considers the population of KEYNOTE-091 and in particular participants in PD-L1 TPS <50% subpopulation, used as the main source of clinical evidence in this submission, to be younger (mean age 64.3 years) than patients with NSCLC expected to be eligible for pembrolizumab in clinical practice in England. Based on data available on the mean age at diagnosis of all patients with NSCLC in England in 2012 who received surgery, the EAG considers the mean age of patients in clinical practice to be higher than captured in the trial. Clinical experts, advising the EAG, agree that participants in the KEYNOTE-091 trial comprise a younger group compared to patients in clinical practice in England. The EAG notes the background mortality risk is expected to increase with age while any utility benefit expected from longer survival will decrease. EAG clinical experts also noted the cure rate achieved with pembrolizumab is likely to be higher, the younger patients are when they start receiving adjuvant pembrolizumab. As a result, the EAG has concerns over the representativeness of the age of participants in the KEYNOTE-091 trial for clinical practice in England and the potential impact of this on effectiveness results.
What alternative approach has the EAG suggested?	The EAG recommends that the average age of patients in clinical practice based on registry data from all patients with NSCLC receiving surgery in England in 2012, 68.42 years, should be used as the mean starting age in the economic model.
What is the expected effect on the cost-effectiveness estimates?	Correcting this is expected to decrease the cost-effectiveness of pembrolizumab compared to placebo. This is because a higher starting age results in a higher mortality rate for both arms limiting the treatment benefit received from pembrolizumab over placebo.
What additional evidence or analyses might help to resolve this key issue?	n/a; or Using an updated/more recent estimate of the mean age of patients in clinical practice in England could provide a more accurate estimate of the effect of pembrolizumab compared to placebo. Nevertheless, the EAG does not expect this to differ substantially from the current source of evidence identified.

Abbreviations: DFS, disease-free survival; EAG, External Assessment Group; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TPS, tumour proportion score

1.4 The cost-effectiveness evidence: summary of the EAG's key issues

Table 5. Issue 3: Better fitting DFS curves are available and should be used

Report section	Section 4.2.5.1.5
Description of issue and why the EAG has identified it as important	The EAG believes that there is substantial justification for fitting separate types of parametric models to each treatment arm. A justification is required as NICE DSU TSD 14 currently recommends parametric distributions for each treatment arm should be the same unless a case is made for the alternative. The company's current base case uses individual parametric log-normal distributions for DF to LR and DF to DM in both treatment arms. Distant and local recurrences occur at dramatically different rates, as a natural result of the disease. There is no reason not to use alternate distributions for transition to LR and DM if this provides a better fit. In the pembrolizumab arm, there is significant evidence of treatment waning, which is not accounted for using the company's model selection. The EAG requested treatment waning be implemented by the company, however, they declined to implement this scenario. Nevertheless, selecting alternate DFS curves for pembrolizumab and placebo appears to adequately capture the treatment waning. Treatment waning has previously been accepted for adjuvant treatment of renal cell carcinoma (TA830). The company's current assumptions grant patients in the pembrolizumab arm a noticeable long-term benefit, which does not seem reasonable given the data available. The EAG selected curves provide a lower MSE and a visually better fit. Prior submissions in this area, TA761 and TA823, used differential cure timepoints to account for this uncertainty.
What alternative approach has the EAG suggested?	The EAG base case uses exponential for DF to LR and log-normal in DF to DM for the pembrolizumab arm. In the placebo arm the EAG uses generalized gamma for DF to LR and gompertz for DF to DM.
What is the expected effect on the cost-effectiveness estimates?	The use of the EAG's preferred assumption significantly decreases the cost-effectiveness of pembrolizumab compared to placebo.
What additional evidence or analyses might help to resolve this key issue?	Post-5-year data showing either continued benefit from having received pembrolizumab or confirming that the treatment wanes to align with placebo patients shortly after this 5-year period.

Abbreviations: DF, disease-free; DM, distant metastases; DSU, Decision Support Unit; EAG, External Assessment Group; LR, local-recurrence; MSE, mean squared errors, NICE, national institute for clinical excellence; TSD, technical support document.

Table 6. Issue 4: There is significant uncertainty in the trajectory of patients post-recurrence due to limitations of the model structure and lack of available trial data.

Report section	Sections 4.2.5.1.5, 4.2.5.3.2

Description of issue and why the EAG has identified it as important	There is insufficient trial data from KEYNOTE-091 to inform transitions for patients who have recurred. The company accounts for this by using Medicaid registry data for locally-recurred patients and trial data from relevant subsequent treatments for patients with distant metastases. However, using these data in the pembrolizumab arm results in significant deviation from the trial OS results. In order to closer match the OS results from the trial a multiplier, for each treatment, was calculated for the transitions rates for recurred patients, to calibrate the model OS curve. This allowed model outcomes to better match the trial results for pembrolizumab and placebo. All recurred transitions had to be modelled assuming exponential distribution as the model did not allow for time-varying transition probabilities post-recurrence. In summation, these stacked assumption lead to significant uncertainty in the transition rates post-recurrence.
What alternative approach has the EAG suggested?	Given the time constraints, there is no alternative approach available to pursue.
What is the expected effect on the cost-effectiveness estimates?	This issue makes cost-effectiveness estimates uncertain but does not reveal a clear bias in one direction.
What additional evidence or analyses might help to resolve this key issue?	A partitioned survival model or adapting the current model to allow for time-dependent transitions in recurred patients would allow different modelling methods and further investigation of the IPD used to inform transitions in these states.
Abbreviations: DF, disease-free; EAG, External Assessment Group; OS, overall survival.	

Table 7. Issue 5. Limiting calibration to 5 years

Report section	4.2.5.3.2
Description of issue and why the EAG has identified it as important	The company's expert advisory board recommended that the calibration of the treatment effect should be capped at 5 years. This intuitively is justified as the calibration multiplier is a highly simplified method of forcing the model OS outcome to match the trial OS. As no significant trial data for OS is available after 5 years it is unreasonable to continue making these matching adjustments.
What alternative approach has the EAG suggested?	Remove the calibration effect at 5 years.
What is the expected effect on the cost-effectiveness estimates?	Correcting this will decrease the cost-effectiveness of pembrolizumab when compared to placebo as the calibration is significantly more beneficial for the active treatment.
What additional evidence or analyses might help to resolve this key issue?	Post 5-year trial data showing the calibration remains necessary.
Abbreviations: EAG, External Assessment Group; OS, overall survival.	

Table 8. Issue 6. I/O ineligible patients uncalibrated

Report section	4.2.5.3.2

Description of issue and why the EAG has identified it as important	The EAG believe it is implausible that I/O ineligible patients in the pembrolizumab arm have poorer efficacy than I/O eligible patients in the placebo arm. This outcome appears to be the result of the model calibration calculating a standard multiplier to apply to all treatment transitions, for each treatment.
What alternative approach has the EAG suggested?	Remove the calibration for I/O ineligible patients and recalibrate.
What is the expected effect on the cost-effectiveness estimates?	Correcting this will increase the cost-effectiveness of pembrolizumab versus placebo. This is because the benefit that would have gone to I/O ineligible patients is apportioned to I/O eligible patients once the model is recalibrated. I/O eligible patients, post-adjuvant pembrolizumab, are less likely to progress and therefore have improved quality of life.
What additional evidence or analyses might help to resolve this key issue?	Greater trial data for recurred patients.

Abbreviations: EAG, External Assessment Group; I/O, immunotherapy

Table 9. Issue 7: Utility value for DF used by company, excluding grade 1/2 adverse events, is higher than general population.

Report section	Section 4.2.6.1
Description of issue and why the EAG has identified it as important	The utility value used by the company for patients in the disease-free health state (0.852) is higher than the general population, which the EAG consider to be implausible. Clinical experts to the EAG stated that following invasive treatments, they would not expect patients to have the same HRQoL as general population and can experience lifelong consequences.
What alternative approach has the EAG suggested?	The EAG consider the utility value derived from KEYNOTE-091, which includes grade 1/2 adverse events (0.806), to be more appropriate for the base-case analysis.
What is the expected effect on the cost-effectiveness estimates?	The EAG's analyses using the alternative value for disease free utility resulted in a moderate increase in the ICER.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that their preferred approach resolves the issue.

Abbreviations: EAG, External Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost effectiveness ratio.

1.5 Additional issues: summary of the EAG's view

A number of additional issues were identified. These have a less significant impact on results than key issues identified in section 1.1 but they still represent areas of uncertainty or required the EAG to make changes to the economic model.

1. The company uses the ITT base case patient characteristics. The EAG have updated the model to reflect the target population (PD-L1 <50%) from the KEYNOTE-091 trial.

2. Age and percent female were not varied in the PSA and no input option for SE for these values was included in the model.
3. NHSE stated that Q6W dosing for pembrolizumab would likely be preferred by EAG, although patients may initially start on Q3W to test for toxicity. Pembrolizumab was assumed to be dosed at Q3W 25% of the time and Q6W 75%.
4. EAG prefer use of the full KM curve for time on treatment and relative dose intensity (RDI) for pembrolizumab, in line with data informing treatment effectiveness.
5. Second line distant metastases treatments were updated based on EAG clinical expert advice.
6. A value for end-of-life costs for cancer patients is available from PSSRU. The EAG consider this more appropriate than the source used by the company.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 10 presents the EAG's preferred assumptions. For further details of additional sensitivity analyses done by the EAG, see Section 6.3 and 6.4. The EAG notes that these results are based on list prices for all comparators/subsequent treatments. A separate confidential appendix has also been provided by the EAG.

Table 10. EAG preferred assumptions and cumulative impact on the ICER

Preferred assumption	Section in EAG report	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
Company base case post clarification		[redacted]	[redacted]	[redacted]
PD-L1 <50% subpopulation baseline characteristics used	Section 4.2.2.1	[redacted]	[redacted]	[redacted]
Baseline age 68.4	Section 4.2.2.1	[redacted]	[redacted]	[redacted]
Q6W dosing for 75% of pembrolizumab patients	Section 4.2.3.1	[redacted]	[redacted]	[redacted]
DFS for pemb = exp/log-normal DFS for placebo = gengam/gomp	Section 4.2.5.1.5	[redacted]	[redacted]	[redacted]
Calibration limited to 5 years	Section 4.2.5.3.2	[redacted]	[redacted]	[redacted]
I/O ineligible patients not calibrated	Section 4.2.5.3.2	[redacted]	[redacted]	[redacted]
Full KM for ToT	Section 4.2.7.7	[redacted]	[redacted]	[redacted]
Alternative 2nd line distant metastatic treatment costs	Section 4.2.7.7	[redacted]	[redacted]	[redacted]
PSSRU end of life cost	Section 4.2.7.7	[redacted]	[redacted]	[redacted]

DF utility include grade 1 and 2 AEs	Section 4.2.6.4	[redacted]	[redacted]	[redacted]
Recalibration		[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; DFS, disease free survival; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; I/O, immunotherapy; KM, Kaplan Meir; QALY, quality-adjusted life-year; ToT, time on treatment.

2 Introduction and background

2.1 Introduction

This report contains the External Assessment Group's (EAG's) critique of the clinical and cost-effectiveness evidence submitted for the Single Technology Appraisal (STA) of pembrolizumab (KEYTRUDA®; Mark Sharp & Dohme UK Ltd.) as adjuvant treatment for adults with non-small cell lung cancer (NSCLC) who are at high risk of recurrence following complete resection and platinum-based chemotherapy.

2.2 Background

Lung cancer, characterised by malignant cells forming in the tissue of the lungs, is the third most common cancer and the most common cause of cancer death in the UK, accounting for 21% of all cancer deaths between 2017 and 2019.[2] It can be divided into two main types based on biology, treatment and prognosis: NSCLC and small cell lung cancer (SCLC), with NSCLC accounting for 80 to 85% of lung cancer cases in the UK.[3]

NSCLC is a type of epithelial lung cancer that, according to its site of origin, can be further classified into three main histological sub-types of adenocarcinoma, squamous cell carcinoma and large-cell carcinoma.[4] Older age and cigarette smoking represent the main risk factors for lung cancer, with median age for NSCLC at diagnosis being 74 years and smoking accounting for 72% of lung cancer cases in the UK.[5, 6] Nevertheless, people who have never smoked can develop lung cancer.[7]

An estimated 57,200 people who had been previously diagnosed with lung cancer were alive in the UK at the end of 2010.[8] Based on diagnoses registered by the Rapid Cancer Registration Dataset (RCRD), in 2021, 34,478 patients were diagnosed with lung cancer in England.[6] Incidence has reportedly been greater in males compared to females with 52% and 48% of lung cancers occurring in males and females, respectively, with incidence rates in the UK being the highest in people aged 85 to 89 years.[8]

NSCLC is most commonly staged using the Tumour-Node-Metastasis (TNM) system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), according to the primary tumour size and extent (T), location of involved lymph nodes (N) and presence of distant metastases (M).[9, 10] Currently, the eight edition of stage classification is used, although tumour staging in the trial informing the current submission was based on the seventh edition. Tumour staging based on the seventh and eight edition of the stage classification is displayed in Table 11 below. [11, 12]

Table 11. Stage classification according to the seventh and eight edition of TNM staging of lung cancer (reproduced from Table 3 in the company submission)

Stage group	TNM staging (7th edition)	TNM staging (8th edition)
0	(TisN0M0)	(TisN0M0)
IA	T1a/T1bN0M0	T1a/T1b/T1cN0M0 T1(mi)N0M0
IB	T2aN0M0 (T>3 to 5cm)	T2aN0M0 (T>3 to ≤4cm)
IIA	T1a/T1bN1M0 (T1a ≤2cm) (T1b>2 to 3cm) T2aN1M0 (T>3 to 5cm) T2bN0M0 (T>5 to 7cm)	T2bN0M0 (T>4 to ≤5cm)
IIB	T2bN1M0 (T>5 to 7cm) T3N0M0	T1/T2N1M0 T3N0M0
IIIA	T1/T2N2M0 T3N1/N2M0 T4N0/N1M0	T1/T2N2M0 T3N1M0 T4N0/N1M0
IIIB	T4N2M0 Any T, N3, M0	T1/T2N3M0 T3/T4N2M0 T3/T4N3M0 (stage IIIC)
IV	Any T, Any N, M1a/M1b	Any T, Any N, M1a/M1b Any T, Any N, M1c
Stage IB (T2a ≥4 cm), II or IIA NSCLC under the AJCC 7th edition is equivalent to stage IIA through IIIB (N2) under the AJCC 8th edition.		

Staging of lung tumours (I, II, III or IV) resulting from the combination of TNM descriptors is based on patient history, physical examination in combination with laboratory and radiological findings (clinical staging) and tissue sampling from biopsy (pathological staging). Staging determines prognosis and optimal management strategy.[10, 12] Tumours at stages I, II, III have better prognosis than those diagnosed at metastatic stage (stage IV). Despite the availability of treatment with curative intent for early-stage lung cancer, patients often experience local/regional recurrence or distant metastasis.[13] Even at an early stage, the risk of recurrence, either local, regional or distant is high (45%, 62% and 76% of patients with stage IB, II and III, respectively).[14] The majority of recurrences tend to be distant, while local or regional recurrences can also further progress to distant metastasis.[15] This has a substantial impact on patients' lives as there are no curative treatment options following recurrence with a distant metastasis.

Despite progress in diagnosis and availability of treatments, 5-year survival of NSCLC remains poor (26.3%).[1] Although 5-year survival improves the earlier lung cancer is detected (see Table 12 below), a need for treatments that reduce the risk of recurrence and the rate of disease progression, and increase the rate of survival remains.

Table 12. One-year and five-year net survival for adults diagnosed with lung cancer between 2016 and 2020 (reproduced from Table 5 in the company submission)

1-year age-standardised survival (%)				
Stage I	Stage II	Stage III	Stage IV	All stages
88.1	75.8	52.6	22.5	44.9
5-year age-standardised survival (%)				
67.8	49.1	24.9	8.8	26.3

Source: NHS Digital 2023[1]

Section B.1.3 of the company submission (CS) provides an overview of NSCLC. Based on advice from the EAG's clinical experts, the CS presents an accurate overview of the health condition, clinical presentation, its progression, disease burden and epidemiology.

2.2.1 Positioning of pembrolizumab for NSCLC in the UK treatment pathway

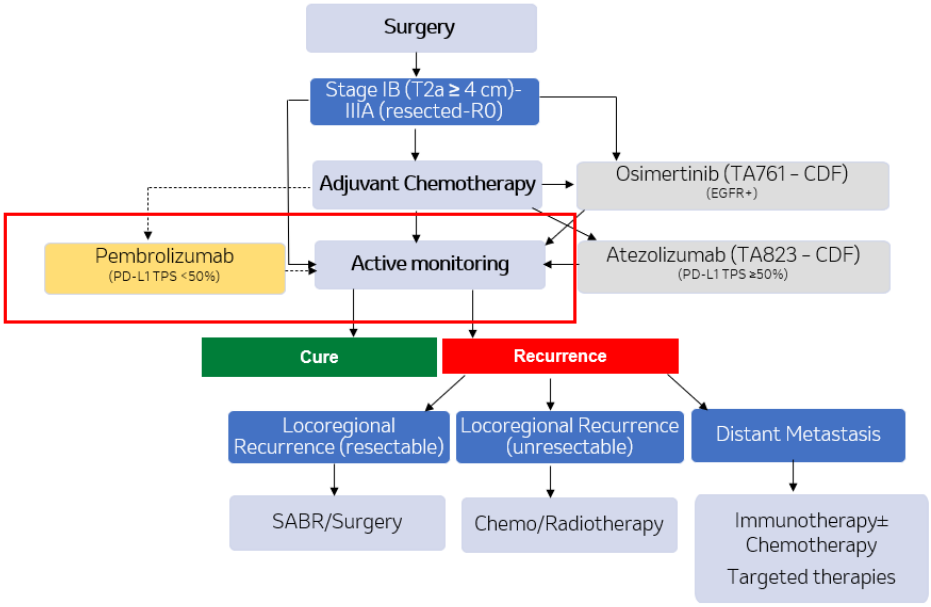
The current treatment pathway for NSCLC and the company's positioning of pembrolizumab are presented in Section B.1.3.2 of the CS. In early-stage NSCLC (stages I-IIIA) the main treatments of choice are offered with curative intent.[16] Following confirmation of diagnosis and staging of NSCLC, usually via contrast-enhanced chest (CT) scan or in some cases biopsy or further imaging (such as PET-CT or MRI scan), surgery is the preferred treatment option for tumours deemed resectable for patients in which radical treatment is considered suitable, based on their fitness level.[6] Despite the curative intent of surgery and the majority of surgical procedures reaching complete resection (R0), a substantial risk of recurrence due to the presence of preoperative micro-metastasis remains.[13, 17] Thus, adjuvant chemotherapy following surgery, is an additional treatment option offered as part of treatment to achieve a cure. Suitability for adjuvant chemotherapy often depends on pre-existing comorbidity, time from surgery and patient choice. This has been confirmed by two of the EAG's clinical experts who have, however, highlighted that the uptake of adjuvant chemotherapy in clinical practice in the UK has not been high, with many patients concerned about toxicity. As confirmed by EAG clinical experts, surgery and adjuvant chemotherapy are followed by active monitoring that usually consists of CT scans at regular intervals, which can vary across centres for example from every 3-6 months to 12-24 months, and which become less frequent after the first year.

The company highlights that there are no additional adjuvant treatments available as part of established clinical management for people who undergo surgical resection, although osimertinib and atezolizumab are available for use through the Cancer Drugs Fund (CDF) for patients with epidermal growth factor receptor (EGFR) mutation-positive NSCLC and patients whose tumours express programmed death-ligand 1 (PD-L1) tumour proportion score (TPS) >50%, respectively. Feedback from NHS England indicates that if osimertinib is approved for routine commissioning,

then this would be the adjuvant treatment used in clinical practice for all EGFR mutation positive patients, as opposed to pembrolizumab.

The company presented an overview of the current treatment pathway depicting the proposed positioning of pembrolizumab within the treatment pathway (see Figure 1 below [CS, Figure 3])

Figure 1 Company's proposed positioning of pembrolizumab relative to the current treatment pathway (reproduced from CS, Figure 3)



Note: Tumour staging is based on TNM staging AJCC 7th edition used in the KEYNOTE-091 trial.
Abbreviations: CDF: Cancer Drugs Fund; EGFR: Epidermal Growth Factor Receptor; NSCLC: Non-small cell Lung cancer; PD-L1: programmed death-ligand 1; TPS: tumour proportion score.

In line with its marketing authorisation, pembrolizumab is expected to be used as an adjuvant therapy for patients with NSCLC at high risk of recurrence (stage IB [T2a ≥4 cm] to III A under AJCC 7th edition), following complete surgical resection and adjuvant chemotherapy. The company positions pembrolizumab in clinical practice, in the subpopulation with PD-L1 biomarker expression with less than 50% TPS. This is in line with the results of the phase 3 KEYNOTE-091 trial informing the current submission, which demonstrate greater effectiveness in the PDL-1 TPS <50% subpopulation. It also reflects the population in the adjuvant setting with higher unmet medical need with no adjuvant treatment options beyond chemotherapy available. In addition, the company considers that in patients with PD-L1 TPS ≥50%, it is unlikely that pembrolizumab will become the preferred treatment option with its efficacy over atezolizumab, currently recommended for use under the CDF, being uncertain.

In absence of any other adjuvant treatment options in the subpopulation with PDL-1 TPS <50%, the only comparator considered by the company to be relevant for pembrolizumab was active monitoring. The EAG's clinical experts agreed with the company's outline of the treatment pathway confirming there are no other treatments routinely given for this group of patients. However, in agreement with the company's clinical experts, the EAG's clinical experts also highlighted the results of KEYNOTE-091 in the PD-L1 TPS ≥50% subpopulation contradicted clinical expectations. In the CS, the company stated that this is likely to be due to an ''overperforming'' control arm in the ≥50% subpopulation. The EAG, considered there was no evidence to support this was the case, as opposed to, for example, the control arm in the PD-L1 TPS <50% subpopulation underperforming and asked that the company provide evidence for the above claim. In response to clarification questions, the company specified that 'better-than-expected' outcomes were observed in the control arm of the PD-L1 TPS ≥50% subpopulation that did not reflect what has been in other trials in the adjuvant setting.[18] The EAG notes that the company acknowledged that apart from the overperformance of the placebo group, results being due to an imbalance in unknown factors such as molecular biomarkers between treatment groups could not be ruled out. This is **Key issue 1** referenced in Section 1.1. See Section 3.2 for further discussion of the company's choice to focus on the PDL-1 TPS <50% subpopulation.

Following recurrence, treatment options including surgery: chemotherapy/radiotherapy and immunotherapy, depend on the type of recurrence (resectable or unresectable locoregional recurrence or distant metastasis). The EAG's clinical experts broadly agreed with the company's treatment pathway following recurrence but highlighted the preferred option will be determined based on the histology of the cancer, the timing of recurrence (e.g. whether it occurred >18 months after the initial diagnosis) and further testing (biopsy) to confirm whether a tumour constitutes recurrence, or a new tumour.

2.3 Critique of the company's definition of the decision problem

A summary of the final scope issued by NICE, together with the company's rationale for any deviation from this, is provided in Table 13. Key differences between the decision problem addressed in the CS and the final scope are discussed in greater detail in the sections that follow below. The EAG considers the main difference between the decision problem specified by the company and the NICE final scope is in the population chosen as the focus of the CS – the company seeks approval in the subpopulation whose tumours express PD-L1 with less than 50% (0–49%) TPS (PD-L1 TPS <50% subpopulation). The EAG considers another key difference between the decision problem and the NICE final scope is in the comparators – the company considered established

clinical management without pembrolizumab (active monitoring) to be the only relevant comparator for pembrolizumab as an adjuvant treatment.

Table 13. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with NSCLC who have undergone complete surgical resection with or without adjuvant chemotherapy	Adults with NSCLC who have undergone complete surgical resection after adjuvant chemotherapy and whose tumours have PD-L1 biomarker expression of less than 50%	Pembrolizumab was approved by the MHRA in the following restricted indication: "*Adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy*.". MSD is seeking reimbursement in the subpopulation whose tumours express PD-L1 with less than 50% tumour proportion score (PD-L1 TPS <50% subpopulation). Based on clinicians' feedback, pembrolizumab would most likely not be used in the subpopulation whose tumours have PD-L1 biomarker expression with at least a 50% tumour proportion score (PD-L1 TPS ≥50%) due to uncertainties associated with the efficacy evidence in these patients compared to available treatments. The submission covers the subpopulation with higher unmet need that can benefit the most from an	The EAG considers the focus of the CS on adults with NSCLC who have undergone complete resection after adjuvant chemotherapy and the exclusion of those without adjuvant chemotherapy that were included in the NICE final scope to be in line with the marketing authorisation for pembrolizumab.[19] The EAG considers the company's choice to narrow the population within the marketing authorisation addressed in the CS to the PD-L1 TPS <50% subpopulation to be reasonable, in light of efficacy evidence and clinicians' feedback. In terms of baseline characteristics, the EAG's clinical experts considered patients in the proposed subpopulation from KEYNOTE-091 trial potentially comprised a younger population than expected in clinical practice in England. See Section 2.3.1 for further discussion.

			additional adjuvant option given the lack of treatments available.	
Intervention	Pembrolizumab	Pembrolizumab	N/A	The treatment regimen for pembrolizumab in the clinical evidence and economic model are consistent with the marketing authorisation for pembrolizumab but with an every six weeks (Q6W) dosing schedule potentially being more common than an every three weeks (Q3W) dosing schedule assumed by the company and used in the clinical evidence.[19, 20] See Section 2.3.2 below for further discussion.
Comparators	Established clinical management without pembrolizumab (that is, active monitoring) Platinum doublet chemotherapy Durvalumab (subject to NICE appraisal) For people whose tumours express PD-L1 with at least a 50% tumour proportion score Atezolizumab after adjuvant platinum-based chemotherapy (subject to NICE appraisal) For people whose tumours have an EGFR genetic alteration	Established clinical management without pembrolizumab (that is, active monitoring)	N/A Platinum doublet chemotherapy is not considered a relevant comparator since, as per Marketing Authorisation, the population eligible for pembrolizumab should receive adjuvant platinum-based chemotherapy after surgery and prior to treatment with pembrolizumab as part of the curative treatment. The peri-adjuvant treatment with durvalumab is not considered a relevant comparator as the patients eligible for	The EAG notes that the company considers established clinical management without pembrolizumab to be the only relevant comparator for pembrolizumab. The EAG notes that is in line with the marketing authorisation with platinum doublet chemotherapy received as adjuvant treatment prior to pembrolizumab. The EAG notes that the marketing authorisation for pembrolizumab is broader than the company's proposed positioning for the subpopulation with PD-L1 TPS <50% and agrees atezolizumab is not a relevant comparator for the subpopulation forming the focus of the CS. Based on clinical expert advice the EAG agrees

	Osimertinib (subject to NICE appraisal)		pembrolizumab, based on the study design of the pivotal trial (KEYNOTE-091/PEARLS), would not receive immunotherapies prior to surgery and therefore pembrolizumab as adjuvant treatment cannot be compared with peri-adjuvant immunotherapies. Also, while participants in the KEYNOTE-091 trial have been randomised after successful completion of a radical treatment plan, in the perioperative setting participants are randomised prior to initiation of the radical treatment plan. The decision point in the clinical pathway is therefore not the same between the trials, the KEYNOTE-091 population being a downstream subset of those included in trials of peri-adjuvant treatment. Also, since the NICE appraisal for durvalumab [ID6220] is currently ongoing [21], durvalumab is not considered standard of care. It is our understanding that atezolizumab [TA823] [22] and osimertinib [TA761] [23] are	no other comparators are relevant, with durvalumab not being considered part of standard care and atezolizumab and osimertinib currently being recommended under the CDF. See Section 2.3.3 below for further discussion.

			recommended under the CDF and, therefore, they cannot be considered relevant comparators in this appraisal in the respective population in which have been recommended under the CDF. Also, pembrolizumab is not expected to be used in the populations in which atezolizumab and osimertinib received their respective NICE recommendation.	
Outcomes	Disease-free survival Event-free survival Overall survival Adverse effects of treatment Health-related quality of life	Disease-free survival Overall survival Adverse effects of treatment Health-related quality of life	The pivotal trial (KEYNOTE-091) informing this submission assessed DFS which is defined as the time from randomization to either the date of disease recurrence or the date of death which are events that may occur in resected patients. Event-free survival (EFS) is not considered a relevant outcome in the evaluation of an adjuvant treatment. EFS has been utilised in trials evaluating the efficacy of perioperative and neoadjuvant treatments as it measures events such as progression of disease precluding surgery and inability to resect the tumour which cannot be measured in	The EAG notes that the company has presented clinical evidence relevant to each of the outcomes specified in the NICE final scope apart from event-free survival. The outcomes used in the economic model are: Disease-free survival Overall survival Adverse effects of treatment Health-related quality of life (HRQoL) Time on treatment (ToT); this was not part of the NICE final scope but was also included in the company's economic model. See Section 2.3.4 below for further discussion.

			patients who have undergone complete resection before receiving adjuvant treatment.	
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 (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per final scope	NA	The economic analysis adheres to the reference case and reflects the final scope.
Subgroups to be considered	If evidence allows the following subgroups will be considered: • by disease stage • by level of PD-L1 expression	No subgroups have been considered in the submission	The submission already focuses on PD-L1 TPS <50% subpopulation on the basis of clinical opinion around the	The EAG notes that pre-planned subgroup analyses were available for variables including, age, sex, stage and histology. These were presented in the CS, for the Prior Adjuvant

			expected positioning of the technology. Further subgroups not explored for C/E: Subgroups by stage should not be considered separately. Whilst stage was a stratification factor in the KEYNOTE-091 trial (the pivotal trial supporting this appraisal), the sample size of the subgroups by stage in the subpopulation in which MSD is seeking reimbursement would be very small (e.g., 45 and 38 patients with stage IB NSCLC in the pembrolizumab and control arm, respectively), and therefore no valid and reliable conclusions can be drawn about how the effectiveness of the technology might differ across these subgroups. In the licensed population, the confidence intervals around subgroup treatment effects overlapped. Also, current SoC for NSCLC patients after complete surgical resection and adjuvant chemotherapy is the same irrespective of stage of cancer prior to surgery and therefore clinical effectiveness and cost-	Chemotherapy subpopulation of the KEYNOTE-091 trial. Although the population of interest was the subpopulation with PD-L1 TPS <50%, the EAG notes that this constitutes a subgroup of the Prior Adjuvant Chemotherapy subpopulation, which comprises n=726 patients and thus further subgroup analysis within the PD-L1 TPS <50% subpopulation, could result in very small sample sizes, preventing reliable conclusions. especially for stratification factors involving multiple strata such as stage. See Section 2.3.6 below for further discussion.

			effectiveness of the technology in these subgroups would be evaluated in comparison with same SoC. Furthermore, previous adjuvant treatment submissions to NICE e.g. [TA823] have not included analysis of subgroups by stage [22] The submission covers one of the subgroups by PD-L1 status (PD-L1 TPS <50% subpopulation). Therefore, the analysis in any other PD-L1 subgroups (e.g., PD-L1 TPS ≥50) not included in the population proposed in this appraisal is not considered relevant.	
Special considerations, including issues related to equity or equality	N/A	N/A	N/A	None listed in the NICE final scope.

Abbreviations: CDF, Cancer Drugs Fund; CS, company submission; EAG, External Assessment Group; HRQoL, Health-related quality of life; MSD, Mark Sharp & Dohme; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; Q3W, every three weeks; Q6W,every six weeks; SoC, Standard of care; ToT, Time on treatment; TPS, tumour proportion score.

2.3.1 Population

The EAG considers the company's choice to exclude adults with NSCLC who have undergone complete resection without adjuvant chemotherapy – included in the NICE final scope – and to only address those with prior adjuvant chemotherapy in the decision problem to be reasonable as it reflects the population covered in the marketing authorisation for pembrolizumab.

The EAG notes that, although the NICE final scope covers the marketing authorisation population irrespectively of PD-L1 expression, the company's proposed population is narrower than the technology's marketing authorisation, focusing on the subpopulation whose tumours express PDL-1 with less than 50% (0–49%). Considering clinical findings suggest the PD-L1 <50% subpopulation, rather than the PD-L1 ≥50% subpopulation, reflects where pembrolizumab provides the most clinical benefit compared to active monitoring; in addition to clinical opinion on current uncertainties surrounding the benefit of pembrolizumab over atezolizumab, a treatment option available for the PD-L1 TPS ≥50% subpopulation via the CDF; the EAG considers the company's choice to seek approval in the subpopulation forming the focus of the CS to be reasonable. However, the EAG has concerns over this choice potentially being data driven. See Section 3.2 for detailed discussion. In addition, clinical experts advised the EAG that findings have been contrary to current knowledge on immunotherapies where the magnitude of the benefit is generally correlated to the level of PD-L1 expression.[24] Moreover, they noted the mechanism underpinning a greater clinical benefit of pembrolizumab as an adjuvant treatment in the PD-L1 TPS <50% subpopulation is not yet understood. This is **Key issue 1** referenced in Section 1.1.

The KEYNOTE-091/PEARLS trial (n=1,177), henceforward referred to as KEYNOTE-091, was a randomised, triple-blinded, placebo-controlled, multicentre trial evaluating the efficacy and safety of adjuvant pembrolizumab versus placebo in participants with Stage IB (T2a ≥ 4cm), II or IIIA (AJCC 7th edition) NSCLC who have undergone complete resection followed by standard adjuvant chemotherapy where appropriate as per relevant local guidelines.[25, 26] The PD-L1 TPS <50% subpopulation of the KEYNOTE-091 trial (n=726), defined as adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy and whose tumours express PD-L1 with less than 50% (0–49%) TPS, comprised the main source of clinical evidence for pembrolizumab in the CS.

The EAG's clinical experts considered patients in the KEYNOTE-091 trial to be largely representative of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy in clinical practice in England with some potential discrepancies (see Section 3.2 for detailed discussion). Based on clinical expert advice, the EAG considers some of the characteristics of the PD-L1 TPS <50% subpopulation differ to those expected in patients in clinical practice. The EAG's clinical experts reported that the mean age [redacted] years in the PD-L1 TPS <50% subpopulation was lower than the average age of patients in clinical practice in England, a large proportion of which is expected to be over 70 years, with the expected increase in background mortality associated with an older population. This is **Key issue 2** referenced in Section 1.1.

The EAG's clinical experts also reported that they would typically see a lower proportion of patients with stage IIIA (AJCC v7) in clinical practice in England but concerns over the representativeness of the population in regards to this characteristic were very minor. In addition, clinical experts advised the EAG that the prevalence of 'never smokers' was slightly higher (approximately 9% higher in the pembrolizumab and 3% in the placebo arm) than seen in patients in clinical practice, a difference that was considered to translate to a lower proportion with squamous histology, the implication of which on the efficacy of pembrolizumab is considered unknown.

In the economic model, the baseline characteristics of patients were based on the overall KEYNOTE-091 trial population. As such, a patient mean age of 64.3 years at baseline was assumed, with 31.7% of the population being female.

2.3.2 Intervention

Pembrolizumab (KEYTRUDA®) is a monoclonal antibody, that as outlined in Table 2 of the CS, binds to the PD-L1 receptor, potentiating an immune response to tumour cells.[20] Pembrolizumab as monotherapy has marketing authorisation for the adjuvant treatment of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy.[20]

This indication in consistent but broader than the CS for this NICE STA (ID3907), which is positioned for the subpopulation with PD-L1 TPS <50%. Pembrolizumab is available in pharmaceutical form as 25 mg/mL concentrate for solution for infusion and the recommended dose is either 200 mg Q3W or 400 mg Q6W administered as an intravenous infusion over 30 minutes.[20] The company reports that for the indication relevant to the current appraisal, pembrolizumab is administered for 18 cycles (Q3W), using Q3W as the base case in the economic model. However, clinical experts advised the

EAG, that the dosing schedule can vary across centres, with a Q6W schedule being more common in clinical practice.

Regarding treatment duration, for the indication relevant to the current appraisal, the marketing authorisation specifies that pembrolizumab should be administered until disease recurrence, unacceptable toxicity or for a duration of up to one year.[20] This aligns with the length of follow-up data available from the clinical evidence and the assumptions made in the economic model.

The EAG considers that the dosing regimen of pembrolizumab in the KEYNOTE-091 trial to be consistent with its marketing authorisation, with pembrolizumab administered intravenously at a dose of 200mg every 3 weeks for up to 18 cycles (approximately 1 year). In case of delay in scheduled administration, the treatment could continue beyond 1 year in order to complete the 18 infusions.

2.3.3 Comparators

The NICE final scope lists the following as comparators of interest:

- Established clinical management without pembrolizumab (active monitoring);
- Platinum doublet chemotherapy;
- Durvalumab (subject to NICE appraisal).

For people whose tumours express PD-L1 with at least a 50% tumour proportion score:

- Atezolizumab after adjuvant platinum-based chemotherapy (subject to NICE appraisal).

For people whose tumours have an EGFR genetic alteration:

- Osimertinib (subject to NICE appraisal).

The EAG notes that the company considers the only relevant comparator for pembrolizumab to be established clinical management, that is active monitoring, which as specified in Section B.3.2 in the CS, consists of regular follow-up with clinical visits and scans to monitor disease recurrence. Given the patient subpopulation chosen as the focus of the CS and clinical expert advice, the EAG considers other comparators unlikely to be relevant for the reasons outlined below.

The EAG notes that the company's exclusion of platinum doublet chemotherapy was in line with the marketing authorisation for pembrolizumab, as patients eligible for pembrolizumab should receive

chemotherapy as an adjuvant treatment following surgery and prior to treatment with pembrolizumab.

Based on clinical expert advice that durvalumab is not currently part of established clinical management and being a peri-adjuvant treatment, the EAG has no concerns that it should have been considered a relevant comparator.

Based on the company's proposed positioning of pembrolizumab for people whose tumours express PD-L1 TPS <50%, a narrower population than specified in its marketing authorisation and in the NICE final scope, atezolizumab which is recommended under the CDF for people whose tumours express PD-L1 with at least 50% TPS is no longer a relevant treatment option for the subpopulation forming the focus of the CS. In addition, the EAG agrees that as both atezolizumab and osimertinib are subject to NICE appraisal and currently offered only within the CDF, they are not relevant comparators for pembrolizumab in the population forming the focus of the current appraisal.

In summary, the EAG is not concerned that the company has omitted potentially relevant comparators available in clinical practice in England.

2.3.4 Outcomes

The EAG notes that the company has submitted evidence relevant to each of the outcomes specified in the NICE final scope except for event-free survival (EFS), that was not considered a relevant outcome in the evaluation of adjuvant treatment. The EAG's clinical experts confirmed that EFS is primarily used in the neoadjuvant therapy space where an event before local treatment surgery would need to be captured. The EAG also notes that EFS was not captured in KEYNOTE-091 trial.

The key clinical outcomes informing the current submission were disease-free survival (DFS) and overall survival (OS) and EAG clinical experts confirmed that these are the most relevant outcomes in the adjuvant therapy space.

The EAG notes that time on treatment (ToT), that was not specified in the NICE final scope was also included in the company's economic model. See Section 3.3.5 and Section 4.2.7 for further discussion.

2.3.5 *Subgroups/special considerations*

In addition to the subgroups of PD-L1 expression and disease stage, specified in the NICE final scope, based on input from clinical experts, the EAG notes that several baseline characteristics are meaningful prognostic factors and/or treatment effect modifiers. These include:

- Age: the EAG's clinical experts noted the background mortality risk is expected to increase with age while any utility benefit derived from extending overall survival with pembrolizumab is expected to decrease, with one expert noting the cure rate achieved with pembrolizumab would be expected to be higher in younger patients;
- EGFR mutation status: the EAG's clinical experts noted this could also be a treatment effect modifier but given the large amount of missing data on mutation status in the KEYNOTE-091 trial, it would not be possible to explore;
- Histology;
- Smoking status.

The EAG notes that while outcome data are available for most of these subgroups and were prespecified subgroups in the KEYNOTE-091 trial, they were not explored in the current CS. The company noted that the focus of the present CS in the subpopulation with PD-L1 TPS <50% results in a limited sample size within each subgroup, that can lead to a high degree of uncertainty in the comparison between pembrolizumab and active monitoring. The EAG acknowledges this concern but notes that size of the subgroups will differ for each variable and some meaningful analyses could be possible. Thus, the EAG requested that the company provide subgroup analyses for the primary and secondary outcomes in the PD-L1 TPS <50% subpopulation. See Section 3.3.3.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trials (RCTs) of pembrolizumab and several comparators for people with early-stage non-small cell lung cancer (NSCLC) after complete surgical resection, with or without adjuvant therapy. The SLR was broad and included a range of comparators not relevant to the current appraisal, but only RCTs of pembrolizumab were included in this submission. The EAG considers the SLR methods used by the company to be robust, and the methods were reported in Appendix D of the company submission (CS). Table 14 contains the EAG's assessment of the SLR methods used by the company.

Table 14. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1	**Appropriate**. The following databases were searched on 13 October 2023: • EMBASE; • MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily; • Cochrane Central Register of Controlled Trials; and • Northern Light. The following trial registries were searched: • US National Institute of Health Database (ClinicalTrials.gov); and • EU Clinical Trials Register. In addition, the abstracts of five oncology conferences were searched from 2022 and 2023: • American Society of Clinical Oncology (searched via Northern Light database); • European Society for Medical Oncology (2022 conference searched via Northern Light database, 2023 conference hand searched); • World Conference on Lung Cancer (searched via Northern Light database); • European Lung Cancer Congress (hand searched); and • North America Conference on Lung Cancer (hand searched, years 2020 and 2022). The EAG notes that a keyword database search of Northern Light was performed to identify relevant abstracts for screening from the American Society of Clinical Oncology, European Society for Medical Oncology and

		World Conference on Lung Cancer conferences. The EAG was unable to identify any published records on the coverage and quality of the indexing of Northern Light as a database of conference abstracts but notes a reasonable number of records were identified from each conference. In addition, in response to clarification questions, the company justified the use of the Northern Light database as a valid source of conference abstracts not published as journal supplements and informed the EAG that the search of the Northern Light database was supplemented with hand searches to ensure all relevant conference abstracts have been captured.
Search strategies	Appendix D.1	**Appropriate**. The search terms included an appropriate range of MeSH terms and free text key words. The search was appropriately restricted to include terms relating to surgery or relevant therapies for non-small cell lung cancer after complete surgical resection. No date limit was imposed on the search. The EAG notes the searches were limited to records in the English language, which may miss some relevant non-English language records.
Inclusion criteria	Appendix D.1	**Appropriate**. The inclusion criteria closely matched the final scope issued by NICE.[27] The inclusion criteria included more comparators than listed in the final scope, but eventually only studies of pembrolizumab were included in the CS.
Screening	Appendix D.1	**Appropriate**. An appropriate dual screening approach was used for title and abstract review and for full text review. Disagreements between reviewers were resolved by a third reviewer.
Data extraction	Appendix D.1	**Appropriate**. Data extraction was performed by two independent reviewers, with a third reviewer resolving any discrepancies after reconciliation between the two primary reviewers.
Quality assessment of included study or studies	Appendix D.3	**Appropriate** A quality assessment of studies included in the SLR was performed using the Cochrane risk-of-bias tool 2 (RoB-2) for randomised trials,[28] which the EAG deemed appropriate. The RoB-2 checklist was completed on the outcome level of disease-free survival (DFS). The EAG agrees that it is best practice to complete risk of bias assessments at the level of the individual outcome, but notes that: • No risk of bias assessment was presented in the CS for outcomes other than DFS, e.g., overall survival or health-related quality of life measures; Only a “traffic-light” coloured summary of the risk of bias domains was provided, rather than free-text justification of the risk of bias for individual RoB-2 items. This made it difficult to assess the quality of the risk of bias assessment.

		However, in response to clarification question, the company provided a detailed Cochrane RoB assessment with free-text justifications for DFS, overall survival, time on treatment, adverse events and quality of life (EQ-5D).

Abbreviations: CS, company submission; DFS, disease-free survival; EAG, External Assessment Group; MeSH, medical subject headings; NICE, National Institute for Health and Care Excellence; RoB-2, Cochrane risk-of-bias tool 2.

In the SLR, 14,423 records were identified from database searching and 1,298 from trial registry searches. Of these 2,499 were removed as duplicates, 1,592 were removed as trial registry records without study results and 1,847 were removed as conference abstracts not identified through the prespecified conference search protocol. At title and abstract screening, 9,585 of 9,783 records were excluded, leaving 198 records to enter full-text screening. Of these, 33 records were included in the SLR, and a further 14 records were included from conference searches, bibliography searches and "other author identified materials". Overall, 47 records were included in the SLR from 17 distinct clinical trials. Of these:

- Two RCTs investigated adjuvant immunotherapies after complete resection that were not relevant to the current appraisal;
- 14 RCTs investigated conventional adjuvant chemotherapy; and
- One trial, KEYNOTE-091, was an RCT of pembrolizumab compared to placebo.

The company noted that KEYNOTE-091 was the only study of relevance to this appraisal, which the EAG agrees with, given the focus of the submission on the population of patients with programmed death-ligand 1 tumour proportion score <50% (PD-L1 TPS <50%) after adjuvant chemotherapy.

3.2 Critique of trials of the technology of interest

There was one trial relating to pembrolizumab identified in the company's SLR (Section 3.1). This was KEYNOTE-091 (NCT02504272), a Phase 3, randomised, triple-blinded, placebo-controlled multicentre trial evaluating the efficacy and safety of adjuvant pembrolizumab compared to placebo for reducing recurrence risk in patients with Stage IB (T2a ≥ 4cm)-IIIA (AJCC 7th edition) NSCLC following complete resection with or without adjuvant chemotherapy (where appropriate as per relevant local guidelines).[25, 26]

In the KENOTE-091 trial, adjuvant chemotherapy was not mandatory but considered for patients with AJCC v7 Stage IB (T2a ≥ 4cm) and strongly recommended for Stage II and IIA. As a result, the trial included a proportion of patients who had not received prior adjuvant chemotherapy. Approximately 86% of trial participants in both arms received prior adjuvant chemotherapy. From the overall trial population (n=1,177), the Prior Adjuvant Chemotherapy Population (n=1,010)

represents the population covered by the marketing authorisation for pembrolizumab. Data from the subpopulation of the Prior Adjuvant Chemotherapy Population, with programmed death-ligand 1 (PD-L1) tumour proportion score (TPS) <50% (n=726), referred to as the PD-L1 TPS <50% subpopulation, was deemed relevant for the decision problem and hence formed the focus of the CS. The EAG's clinical experts agreed it was appropriate to focus on this subpopulation (and not the overall trial population which included people without prior adjuvant chemotherapy or the Prior Adjuvant Chemotherapy Population which included people with PD-L1 TPS >50%) considering the company's choice to seek approval of pembrolizumab in people whose tumours express PD-L1 with less than 50% TPS.

The EAG noted that if the PD-L1 TPS <50% subpopulation of people with prior adjuvant chemotherapy was not a pre-specified subgroup in the KEYNOTE-091 trial, the choice to focus and present results for this subgroup *post-hoc* could entail risk of bias. That is because it could be a data-driven decision, potentially overestimating the effectiveness of pembrolizumab over placebo as, as stated in the CS, this population reflects where pembrolizumab provides the most clinical benefit in the adjuvant setting. The EAG asked a clarification question for the company and the company confirmed that the PD-L1 TPS subpopulation was not a prespecified subgroup in the trial. In response to clarification questions, the company noted that adjuvant chemotherapy and PD-L1 TPS 0% vs 1-49% vs ≥50% were stratification factors and pre-specified subgroups strengthening the results for the subgroup of interest. Nevertheless, the company highlighted that despite PD-L1 TPS <50% not being a stratification factor, no substantial imbalances were found in the baseline characteristic between treatment arms, except for smoking, ECOG, histology and ALK status which also appeared imbalanced in the overall trial population as well. The company also noted that the choice to focus on the PD-L1 TPS <50% subpopulation was not data-driven but reflects the population in the adjuvant setting with no adjuvant treatment options beyond chemotherapy available with a high unmet medical need. Although the company suggested the above factors should provide reassurance on the robustness of the results in the PD-L1 TPS <50% subpopulation with prior adjuvant chemotherapy, the EAG considers the focus on the *post-hoc* subpopulation to be a limitation. In addition, the EAG does not consider focusing on the subgroup with prior adjuvant chemotherapy in the KEYNOTE-091 trial to be at risk of bias as it was a prespecified subgroup of the KEYNOTE-091 trial. However, as discussed further in Table 15 below, focusing on a subgroup within this subgroup (the PD-L1 TPS <50% subpopulation) increases the risk of Type I error. This is **Key issue 1** referenced in Section 1.1.

Applicability of the KEYNOTE-091 trial to the decision problem is discussed throughout Section 2.3 and the trial methodology is described in Section B.2.3 of the CS with statistical analysis and critical appraisal described in Sections B.2.4 and B.2.5, respectively. The risk of bias of the KEYNOTE-091 trial, based on the Cochrane risk-of-bias tool for randomised trials (RoB-2)was deemed Low. [29] While the EAG agrees that the risk of bias in a triple-blinded, randomised trial is certainly lower than an open-label trial, the RoB checklist was completed on the outcome level of disease-free survival (DFS), and no risk of bias assessment was presented for other outcomes included in the economic model, such as overall survival (OS) and quality of life. The EAG also noted that free-text justification of the risk of bias for individual RoB items was not provided, and as a result the EAG could not be certain that the assessment of risk of bias as Low was appropriate. Thus, the EAG requested that the company provide a risk of bias assessment for OS, EQ-5D, adverse events (AEs) and time on treatment (TOT) as well as free-text justifications for each item of the RoB checklist for all outcomes. In response to clarification questions, the company provided a detailed Cochrane RoB assessment for all outcomes with free-text justifications and thus the EAG no longer has concerns on the appropriateness of the risk of bias assessment.

The EAG's assessment of the design, conduct, internal validity of the KEYNOTE-091 trial and the representativeness of the trial population is summarised in Table 15 below.

Based on clinical expert advice, the EAG considers that some of the characteristics of the PD-L1 TPS <50% subpopulation, and most importantly the age of participants, are not consistent with NSCLC patients eligible for pembrolizumab in clinical practice in England. Clinical experts advising the EAG noted that participants in the trial were younger than patients in clinical practice and noted that in addition to age being a prognostic factor, due to mortality risk increasing with age, older individuals may have lower tolerability of pembrolizumab than younger individuals. Thus, the EAG asked the company to comment on the representativeness of the age of the subpopulation of interest for patients in clinical practice in England and on whether age can be a meaningful treatment effect modifier. In response to the EAG's clarification question on the age of participants in the subpopulation of interest in the KEYNOTE-091 trial, the company confirmed the view of the EAG's experts that the median age of lung cancer patients in clinical practice is higher. The company estimated the median age of patients at diagnosis in clinical practice in England is 73 years but noted that this estimate was based on patients across all stages of cancer, including stage IV that were not included in the KEYNOTE-091 trial. The EAG notes the mean (SD) age at diagnosis of all patients diagnosed with NSCLC in England in 2012 (n=31,351) was 72.81 (10.90) years, consistent with the

company's estimate of the median age, while the mean (SD) age at diagnosis of those receiving surgery (n=4,850) was 68.42 (9.81) years.[30] Considering the MA for pembrolizumab indicating its use in patients who have received surgery, the EAG decided it was appropriate to use the latter mean age as the EAG base case. See Section 4.2.2 for further discussion. The EAG acknowledges that as noted by the company in response to clarification questions, participants included in the trial were younger and fitter than the average NSCLC patient as this was required to receive surgery and subsequently adjuvant chemotherapy and that this is a common issue present across clinical trials. However, the EAG notes the risk of mortality tends to increase progressively with age, while any utility benefit of treatment is likely to decrease. In addition, two of the EAG's clinical experts noted the cure rate achieved is likely to be higher in a younger population compared to an older population. Thus, the EAG's concerns that the younger age of participants in the trial may have impacted on the effectiveness of pembrolizumab remain. This is **Key issue 2** referenced in Section 1.1.

Table 15. EAG's summary of the design, conduct and analysis of KEYNOTE-091

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	B.2.3.1 in CS	**Appropriate** Patients were randomised in a 1:1 ratio to pembrolizumab 200 mg (n=590) or saline placebo (n=587) administered intravenously every 3 weeks for up to 18 cycles, using a minimisation technique with a random allocation component to ensure 15% of completely random assignments. Randomisation was stratified by disease stage (IB vs II vs IIIA), previous receipt of adjuvant chemotherapy (no adjuvant chemotherapy vs adjuvant chemotherapy), PD-L1 status: negative (TPS=0%) vs weak positive (TPS=1-49%) vs strong positive (≥50%), and geographical region (Western Europe vs Eastern Europe vs the Rest of the world vs Asia).
Concealment of treatment allocation	B.2.3.1 in CS	**Appropriate** Randomisation was conducted using a central interactive voice-response system (Almac Clinical Technologies, Souderton, PA, USA). Participant registration was done centrally at the European Organisation for Research and Treatment of Cancer (EORTC) headquarters (Brussels, Belgium)
Eligibility criteria	B.2.3.1 in CS	**Appropriate** Full details of the eligibility criteria for KEYNOTE-091 overall trial population are available in the CS Table 9. Key inclusion criteria for the PD-L1 TPS <50% subpopulation were: • Adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy and whose tumours express PD-L1 with less than 50% (0-49%) TPS.

Blinding	B.2.3.1 in CS	**Appropriate** KEYNOTE-091 was a triple-blinded, placebo controlled RCT with participants, investigators, those collecting or analysing the data, representatives of the Sponsor, EORTC staff, all masked to the treatment assignment.
Baseline characteristics	B.2.3.1 in CS	**The EAG considers the baseline characteristics of the KEYNOTE-091 PD-L1 TPS <50% subpopulation potentially indicate a younger population than expected in clinical practice in England.** • The EAG's clinical experts noted the median age (range): 64 (35 to 84) years was lower than the average age at which patients expected to be eligible for pembrolizumab are seen in clinical practice in England. The EAG notes that this may have a significant implication on effectiveness due to the expected increase in background mortality associated with an older population. • The proportion of patients with stage IIIA (as per AJCC v7) at baseline was higher than expected. • The EAG's clinical experts noted that the proportion of never smokers was slightly higher than expected, noting that this also reflects on histology of tumours. • The proportion of patients with squamous histology was lower and the proportion with non-squamous histology was higher compared to clinical practice in England due to the larger prevalence of never smokers. • The EAG's clinical experts raised that the proportion of patients EGFR and ALK mutation positive status was slightly higher than expected compared to patients in clinical practice in England, noting that patients who are EGFR positive would not be treated with adjuvant chemotherapy or immunotherapy in clinical practice. However, the EAG notes that the accuracy of these data cannot be validated as the status of the majority of patients in the trial was unknown.
Dropouts	Appendix D.2 of the CS	**High although reasonable considering the duration of follow-up (median duration of follow-up for participants in the overall population was [redacted] months in the pembrolizumab group and [redacted] months in the placebo group) but discontinuation data specific for the PD-L1 TPS <50% subpopulation were not provided.** Of the 1,177 participants randomised in the trial, and included in the ITT population, 590 were assigned to pembrolizumab and 580 were assigned to placebo. The proportion of participants who completed study medication was lower in the pembrolizumab group (51.7%) compared with the placebo group (65.6%). The most common (>15%) reasons for study medication discontinuation in the pembrolizumab group compared with the placebo group were study medication toxicity (19.7% vs 3.8%, respectively) and recurrence/relapse/death due to disease progression (12.4% vs 21.9%, respectively). The proportion of the participants in each treatment arm who were ongoing in the study was similar (pembrolizumab group [72.7%]; placebo group [70.7%]. The most common reason for study discontinuation in the pembrolizumab group and the placebo group was death (23.1% vs 26.2%, respectively).

Statistical analysis		
Sample size and power	Section B.2.6 in CS	**Appropriate for the overall trial population but smaller sample size for the subpopulation may limit the robustness of conclusions.** It was calculated that approximately 1,180 participants would need to be randomized in a 1:1 ratio in the pembrolizumab and the placebo arm. Based on a target number of ~551 events at final analysis, the study was designed to have ~86% power at alpha=1.25% (one-sided) and ~92% power at alpha=2.5% (one-sided) to detect 25% reduction in DFS (HR=0.75) in the overall population. The EAG considers the PD-L1 TPS <50% subpopulation of the overall trial population to be appropriate for addressing the decision problem but has some concerns about its relatively smaller sample size (n=726) compared to the sample size needed for the study to have sufficient power based on initial power calculation for the overall trial population. The EAG notes that as a result of focusing on a smaller subsample of the original sample, power is reduced and there is a risk of Type I error. The EAG considers that the results for the PD-L1 TPS<50% may be valid but the potential for a Type I error may mean they are just due to chance.
Handling of missing data	Sections 10.5 and 16.1.9.2 KEYNOTE-091 IA3 Clinical study report	**Appropriate** No imputation of missing data was reported. DFS missing data were handled according to prespecified censoring rules. For OS, censoring occurred at the date a participant was last known to be alive. [redacted]
Outcome assessment	Section B.2.4 in CS	**Reasonable** Efficacy analyses of the primary and secondary endpoints (DFS and OS) were performed in the intention-to-treat (ITT) population consisting of all participants randomly assigned to a treatment group. These analyses were applicable to the PD-L1 TPS <50% subpopulation, that was not a pre-defined subgroup, but were the focus of the CS as well as for the Prior adjuvant chemotherapy population (population covered by the MA). Analyses of quality of life were performed in the PRO full analysis set (FAS) population, consisting of all randomised participants who received at least one dose of study treatment and completed at least one assessment for the respective PRO questionnaire/scale anytime period under investigation. Safety was assessed in the 'all participants-as-treated population' (APaT) consisting of all randomly assigned participants who received at least one dose of study treatment. Adverse events were presented for the Prior Adjuvant Chemotherapy population and for the Overall Population, as data for the PD-L1 TPS <50% subpopulation were not available. The EAG's clinical experts agreed with the company that no substantial differences in

		the safety profile were expected between the two populations and noted the larger sample size of the overall population compared to the subpopulation of interest, is likely to provide a more accurate/robust representation of any differences in safety between pembrolizumab and placebo. Thus, the EAG did not request a breakdown of adverse events in the PD-L1 TPS <50% subpopulation at clarification.

Abbreviations: APaT, all participants-as-treated population; CS, company submission; DFS, disease-free survival; EAG, External Assessment Group; EGFR, epidermal growth factor receptor; EORTC, European Organisation for Research and Treatment of Cancer; FAS, full analysis set; HRQoL, health-related quality of life; ITT, intention-to-treat; MA, marketing authorisation; OS, overall survival; PD-L1, programmed death-ligand; RCT, randomised controlled trial; TPS, tumour proportion score.

3.3 Critique of the clinical effectiveness analysis and interpretation

In Section B.2.6 of the CS, the company outlines results for primary, secondary and exploratory outcomes of KEYNOTE-091. The data presented are the results of the prespecified interim analysis 3 (IA3) with a database cut-off date of 24-JAN-2023. Results are reported for the PD-L1 TPS <50% subpopulation, in which approval for pembrolizumab is sought, except for adverse events (AEs) where results are presented for the Overall Population of the trial used in the safety analysis. See Section 3.3.5.

All outcomes specified in the NICE final scope were presented in the CS, apart from event-free survival (EFS) that was not measured in the KEYNOTE-091 trial. EAG clinical experts agreed with the company that EFS is not the most relevant outcome in the adjuvant therapy space, with disease-free survival (DFS) being most important. They noted that looking at DFS rather than EFS avoids looking at events occurring before surgery, ensuring that disease-specific recurrences are measured. DFS, the primary outcome of the KEYNOTE-091 trial was used by the company in the economic model to inform transition probabilities. Overall survival (OS), the secondary outcome in the KEYNOTE-091 trial, was also used in the company's model with modelled OS calibrated to match the observed OS. See Section 4.2.5 for more details. The ITT population, comprised of all randomised patients, was used for the efficacy analyses (primary and secondary outcomes).

The median (range) duration of follow-up, defined as the time from randomisation to the date of death or the database cut-off date in the participant is still alive, for the Prior Adjuvant Chemotherapy population was [redacted] months in the pembrolizumab group and [redacted] months in the placebo group. The EAG notes that the duration of follow-up for the subpopulation of interest was not reported in the CS. Follow-up assessments were

performed every twelve weeks during the first year after randomisation, every six months during the second and third year and then yearly for year four and five. Thereafter, the imaging work-up was performed at least yearly up to year ten, with disease recurrence collected beyond the fifth year.

3.3.1 Primary outcome: Disease-free survival

DFS in the KEYNOTE-091 trial was defined as time from randomisation to either the date of disease recurrence or the date of death from any cause (whichever occurred first), with recurrence of disease being a loco-regional recurrence or a distant (metastatic) recurrence or a second primary. NSCLC and second malignancies were considered to be events. DFS was assessed locally by investigator review. If an event of death or disease recurrence did not occur by the time of the last visit, patients were censored at the time of the last examination.[31] The results of DFS are summarised in Table 16.

The EAG notes that the median DFS in IA3 results in the PD-L1 TPS <50% subpopulation was 51.7 months (95% CI: 39.0 to 70.4) in the pembrolizumab group and 34.5 months (95% CI: 23.3 to 46.4) in the placebo group. Median DFS was 17.2 months longer in the pembrolizumab group compared to the placebo group, with 168 (46.3%) and 199 (54.8%) DFS events occurring in each group, respectively. This corresponded to a 28% relative reduction in the risk of disease recurrence or death with pembrolizumab compared to placebo (HR: 0.72, 95% CI: 0.58 to 0.89).

Table 16. Disease-Free survival in the PD-L1 TPS <50% subpopulation (ITT population; reproduced from CS, Table 17)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median DFS* (Months) (95% CI)	DFS Rate at Month 12 in %* (95% CI)	vs. Placebo	
							Hazard Ratio† (95% CI) †	p-Value‡
Pembrolizumab	363	168 (46.3)	11254.7	1.5	51.7 (39.0, 70.4)	78.3 (73.5 to 82.3)	0.72 (0.58, 0.89)	0.00096
Placebo	363	199 (54.8)	10027.2	2.0	34.5 (23.3, 46.4)	69.3 (64.3 to 73.8)	—	—

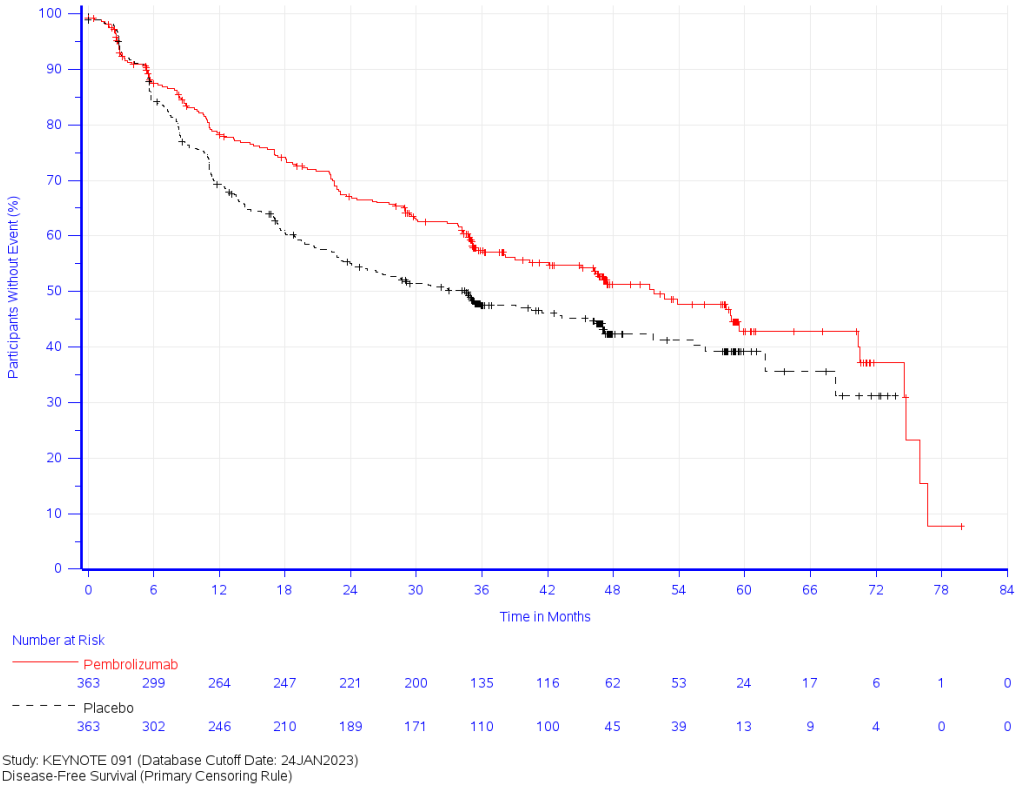
* From product-limit (Kaplan-Meier) method for censored data.

† Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

‡ One-sided p-value based on the Wald Test in the multivariate Cox regression model.

Database Cutoff Date: 24JAN2023

Figure 2. Kaplan-Meir Estimates of Disease-Free Survival in the PD-L1 TPS <50% subpopulation (ITT population; reproduced from CS, Figure 5)



Source: Data on File. KEYNOTE-091 IA3 Statistical Report[32]

Table 17. Summary of DFS Rate Overt Time in the PD-L1 TPS <50% Subpopulation (ITT Population; reproduced from Table 18 in CS)

Estimated DFS rate (95% CI) *	Pembrolizumab (N=363)	Placebo (N=363)
12 Months	[redacted]	[redacted]
18 Months	[redacted]	[redacted]
24 Months	[redacted]	[redacted]
30 Months	[redacted]	[redacted]
36 Months	[redacted]	[redacted]
42 Months	[redacted]	[redacted]
48 Months	[redacted]	[redacted]
54 Months	[redacted]	[redacted]
60 Months	[redacted]	[redacted]

* From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report[32]

The EAG notes that the DFS rate was highest at 12 months in both treatment groups, progressively being reduced in subsequent months. Overall, after the first months of treatment, the rate of DFS was higher in the pembrolizumab group compared to placebo, with the magnitude of the difference being largest at 18 months (based on Table 18 in CS [Table 17 above]).

The most common type of first DFS event in both groups was recurrence. The EAG notes that fewer participants in the pembrolizumab group (participants) experienced disease recurrence compared to placebo (participants). The most frequent type of recurrence reported was distant metastases, which occurred less frequently in the pembrolizumab group (participants) compared with the placebo group (participants). A lower proportion of participants experience local and/or regional recurrence in the pembrolizumab group compared to placebo (. The results on the type of the first DFS event experienced are summarised in Table 18.

Table 18. Disease status in the PD-L1 TPS <50% subpopulation (ITT population; reproduced from Table 20 in CS)

	Pembrolizumab n (%)		Placebo n (%)	
Participants in population	363		363	
Type of First Event in DFS Analysis				
No event	195	(53.7)	164	(45.2)
Event	168	(46.3)	199	(54.8)
Not disease-free at baseline	[redacted]			
Recurrence	[redacted]			
Local and/or regional recurrence	[redacted]			
Distant metastasis	[redacted]			
Both	[redacted]			
New malignancy	[redacted]			
Death	[redacted]			

New malignancy includes the second primary and second malignancies.
Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report. [32]

3.3.2 *Secondary outcome: Overall survival*

OS in the KEYNOTE-091 trial was defined as the time from the date of randomisation to the date of death from any cause. If a death event did not occur during the follow-up period, the patient was censored at the last visit/contact. In the PD-L1 TPS <50% subpopulation, there was a lower number of deaths in the pembrolizumab group (84 [23.1%]) compared to the placebo group (110 [30.3%]) corresponding to HR of 0.73 (95% CI: 0.55 to 0.97). The EAG notes that the median OS in IA3 results was not reached for either treatment group, highlighting the immaturity of OS data. These results are presented in Table 19. In the CS, the company reports that the analysis of OS in the overall population showed a trend towards improvement favouring pembrolizumab compared to placebo with an improvement in OS HR, but that due to the early time of the analysis with respect to OS

(information fraction of approximately [redacted]), the difference between treatment groups was not statistically significant at IA3 (HR: 0.87 [95% CI: 0.69 to 1.10]; p=0.11792).

Table 19. Overall survival in the PD-L1 TPS <50% subpopulation (ITT population; reproduced from CS, Table 21)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS* (Months) (95% CI)	OS Rate at Month 12 in %* (95% CI)	vs Placebo	
							Hazard Ratio† (95% CI) †	p-Value‡
Pembrolizumab	363	84 (23.1)	16271.7	0.5	Not Reached (., .)	95.2 (92.5 to 97.0)	0.73 (0.55, 0.97)	0.01626
Placebo	363	110 (30.3)	15782.4	0.7	Not Reached (., .)	94.7 (91.9 to 96.6)	—	—

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

†Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), adjuvant chemotherapy (yes vs. no), region (Western Europe vs Eastern Europe vs Rest of World vs Asia), histology (squamous vs non-squamous), and smoking status (never vs former/current).

‡One-sided p-value based on the Wald Test in the multivariate Cox regression model.

Database Cutoff Date: 24JAN2023

Figure 3. Kaplan-Meier Estimates of Overall survival in the PD-L1 TPS <50% subpopulation (ITT population; reproduced from CS, Figure 6)

Source: Data on File. KEYNOTE-091 IA3 Statistical Report[32]

Table 20. Summary of OS Rate Overt Time in the PD-L1 TPS <50% Subpopulation (ITT Population; reproduced from Table 22 in CS)

Estimated OS rate (95% CI) *	Pembrolizumab (N=363)	Placebo (N=363)
12 Months	[redacted]	[redacted]
18 Months	[redacted]	[redacted]
24 Months	[redacted]	[redacted]
30 Months	[redacted]	[redacted]
36 Months	[redacted]	[redacted]
42 Months	[redacted]	[redacted]
48 Months	[redacted]	[redacted]
54 Months	[redacted]	[redacted]
60 Months	[redacted]	[redacted]

*From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report[32]

The EAG notes that similar to DFS, the OS rate was highest at 12 months in both treatment groups, progressively being reduced in subsequent months. Overall, after the first months of treatment, the rate of OS was slightly higher in the pembrolizumab group compared to placebo. The placebo group showed a greater reduction in the OS rate overtime, with the magnitude of the difference between groups increasing with the largest observed differences being at 42 and 48 months (based on Table 22 from the CS [Table 20, above]).

However, the EAG is concerned that the results for OS may be confounded by the use of subsequent therapies not routinely used in clinical practice in England and therefore obscuring the extent to which a benefit in OS can be attributed to pembrolizumab. In response to the EAG's clarification questions, the company provided data on the subsequent oncologic therapies received by participants with locoregional recurrence and distant metastases in the PD-L1 TPS <50% subpopulation. These are summarised in Table 21 and Table 22 below.

Table 21. Summary of Subsequent Oncologic Therapies – Participants with Locoregional Recurrence for Disease-free Status (Primary Censoring Rule) Based on Investigator Assessment – PD-L1 TPS < 50% Subpopulation (All-Participants-as-Treated Population; reproduced from Table 6 in company's response to clarification)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]					
Participants who had any subsequent oncologic therapies for NSCLC	[redacted]					
Subsequent drug therapy	[redacted]					
Subsequent radiation	[redacted]					
Subsequent surgery	[redacted]					
Participants could have multiple subsequent oncologic therapies for NSCLC. Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 24JAN2023						

Table 22. Summary of Subsequent Oncologic Therapies – Participants With Distant Metastases for Disease-free Status (Primary Censoring Rule) Based on Investigator Assessment – PD-L1 TPS < 50% Subpopulation (All-Participants-as-Treated Population; reproduced from Table 8 in company's response to clarification)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]					
Participants who had any subsequent oncologic therapies for NSCLC	[redacted]					
Subsequent drug therapy	[redacted]					
Subsequent radiation	[redacted]					
Subsequent surgery	[redacted]					
Participants could have multiple subsequent oncologic therapies for NSCLC. Every participant is counted a single time for each applicable row and column.						

The EAG noted that [redacted] of patients with locoregional recurrence and [redacted] of patients with distant metastases in the KEYNOTE-091 PD-L1 TPS <50% subpopulation received subsequent treatments following pembrolizumab and the EAG is concerned that at least some patients receiving subsequent therapies, received treatments that are not consistent with clinical practice in England. For example, the subsequent therapies participants received following distant metastases included surgery and radiation which, as the EAG's clinical experts noted, are not in line with the treatment pathway presented by the company (see Section 2.2.1), where immunotherapy or chemotherapy are the treatment options following distant metastases. The EAG also notes that the overall proportion of patients with distant metastases in the PD-L1 TPS <50% subpopulation that received subsequent therapies differed considerably between the pembrolizumab ([redacted]) and the placebo ([redacted]) treatment groups and so did the proportion of patients for each type of subsequent therapy (e.g. in people with distant metastases receiving subsequent therapies, radiotherapy occurred much less frequently in the pembrolizumab group [[redacted]] compared to placebo [[redacted]]). Based on advice from its clinical experts, the EAG considers the proportion of patients receiving subsequent therapies to be reasonable, but the treatments received are not always consistent with clinical practice in England and the proportion receiving subsequent therapies between treatment groups being differential, the EAG considers it difficult to predict the resulting impact of this on the findings for pembrolizumab. Thus, the EAG asked the company to comment on any inconsistencies in subsequent therapies. In response to clarification questions, the company noted subsequent therapies were not mutually exclusive and participants may have received multiple subsequent therapies. Although the company emphasised that the majority of cases of surgery and radiation were not targeting the lungs, being surgeries for [redacted] or radiation with palliative intent to target the [redacted] and [redacted] the EAG still has concerns over the generalisability of the trial to clinical practice in England based on the types of subsequent therapies participants received, particularly as surgery and radiation for distant metastases were not included in the economic model.

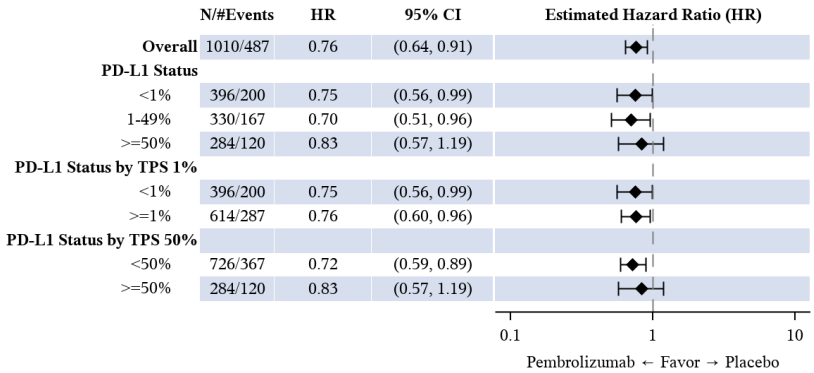
3.3.3 Subgroup analyses

In the CS, it is reported that subgroup analyses were planned in the overall KEYNOTE-091 trial population, to compare DFS and OS by treatment arm for subgroups including:

- Age (<65 vs >65);
- Sex (Male vs Female);
- Race (White vs All Others);
- Region (EU vs non-EU);
- Geographic region (Western Europe vs Eastern Europe vs Rest of the World vs Asia);
- Stage (IB vs II vs IIA) – stratification factor;
- Adjuvant chemotherapy (No vs Yes) – stratification factor;
- Smoking status (Never Smoker vs Former Smoker vs Current Smoker);
- Histology (Squamous vs. Non-squamous);
- ECOG Performance status (0 vs 1);
- EGFR mutation status (No vs Yes vs Uknown);
- PDL-1 Status (<1% vs 1-49% vs ≥50%; <1% vs ≥1%; <1% vs ≥50%) – stratification factor.

In the CS, the company provided forest plots for subgroup analyses of DFS in the Prior Adjuvant Chemotherapy population (MA population), but not for OS or for the PD-L1 TPS <50% subpopulation in which approval is sought. These included a forest plot of DFS by PD-L1 subgroup factors presented in Figure 4 below, where the EAG noted that although small, there was a difference in the DFS hazard ratios between PD-L1 subgroups, with the hazard ratio in 1-49% PD-L1 subgroup being lower compared to the other PD-L1 status subgroups.

Figure 4. Forest Plot for DFS Hazard Ratio – Prior Adjuvant Chemotherapy Subpopulation (ITT Population; reproduced from Figure 9 in CS)



The PD-L1 TPS <50% subpopulation was not a pre-specified efficacy population in the KEYNOTE-091 trial and the company did not provide further subgroup analysis within this subpopulation noting that the small sample size of the subgroups would result in wider confidence intervals and no

meaningful conclusions about the treatment effect in different subgroups. The EAG acknowledges the company's concerns over the sample size but noted that the DFS hazard ratios between PD-L1 subgroups in the Prior Adjuvant Chemotherapy subpopulation differed and that the size of the subgroups will differ for each variable and some meaningful analyses may be possible. Thus, the EAG requested that the company provide results for the DFS and OS subgroup analyses within the PD-L1 TPS <50% subpopulation, including the subgroups of <1% vs 1-49%. These results are presented in Figure 5 and

Figure 6 below.

The EAG notes that the benefit of pembrolizumab over placebo in DFS and OS was consistent across the majority of subgroups and with the results on subgroup analyses in the Prior Adjuvant Chemotherapy population reported in the CS (Figures 8 and 9 in CS). The EAG agrees with the company that results should be interpreted with caution, particularly for the subgroups that were not stratification factors and for OS considering the early time point of the analysis.

Figure 5. Forest Plot of DFS Hazard Ratio – PD-L1 TPS <50% Subpopulation (ITT Population; reproduced from Figure 11 in the company's clarification response)

1. For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment, adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥ 50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), using Wald confidence interval. For other subgroups, analysis is based on Cox regression model with treatment as a covariate using Wald confidence interval.

2. If a subgroup variable has two levels and one level of the subgroup meets any criteria below, then this subgroup variable will not be displayed: (1) if the number of participants in a category of a subgroup variable is less than 50, (2) the number of events in a category of a subgroup variable is zero in one treatment arm, (3) the number of events in a category of a subgroup variable is less than 5 in the pooled arms.

Database Cutoff Date: 24JAN2023

Figure 6. Forest Plot of OS Hazard Ratio – PD-L1 TPS <50% Subpopulation (ITT Population; reproduced from Figure 12 in the company's clarification response)

1. For PD-L1 subgroup, analysis is based on multivariate Cox regression model with treatment, adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥ 50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs Asia), histology (squamous vs. non-squamous), and smoking status (never vs former/current), using Wald confidence interval. For other subgroups, analysis is based on Cox regression model with treatment as a covariate using Wald confidence interval.

2. If a subgroup variable has two levels and one level of the subgroup meets any criteria below, then this subgroup variable will not be displayed: (1) if the number of participants in a category of a subgroup variable is less than 50, (2) the number of events in a category of a subgroup variable is zero in one treatment arm, (3) the number of events in a category of a subgroup variable is less than 5 in the pooled arms.

Database Cutoff Date: 24JAN2023

3.3.4 *Quality of life*

Health-related quality of life (HRQoL) data was available from the KEYNOTE-091 trial. These were obtained using various measures including the EORTC QLQ-C30 Global Health Status/Quality of Life Questionnaire C-30 (QLQ-C30) and EQ-5D. Week 48 was selected as the primary timepoint for the analysis of mean change in HRQoL from baseline. Considering outcome assessment took place every 12 weeks in the first year and Week 48 represents the latest time-point at which participants would still be on treatment, the EAG notes the choice of timepoint was reasonable. In the CS, for the PD-L1 TPS <50% subpopulation, results were presented from the EQ-5D. As discussed further in Section 4.2.6. EQ-5D data were used in the economic model. EQ-5D analyses were performed on the PRO full analysis (FAS) population, comprised by all randomised participants who received at least one dose of study treatment and completed at least one assessment for the respective PRO questionnaire/scale anytime during the period under investigation.

Analysis of the EQ-5D-5L visual analogue scale (VAS) score at Week 48 showed no clinically meaningful changes from baseline in either treatment group. At Week 48, there was a difference in least squares (LS) means of [redacted] [95% CI: [redacted]]. The results for EQ-5D VAS are summarised in Table 23.

Table 23. Analysis of Change from Baseline in EQ-5D VAS to Week 48 in PD-L1 TPS <50% (PRO FAS Population; reproduced from CS Table 24)

	Baseline		Week 48		Change from Baseline to Week 48		
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)*	
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pairwise Comparison						Difference in LS Means* (95% CI)	p-Value*
Pembrolizumab vs. Placebo						[redacted]	[redacted]

* Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, stage (IB vs II vs IIIA), PD-L1 status (≥50% vs 1-49% vs <1%), region (Western Europe vs Eastern Europe vs Rest of World vs Asia), histology (squamous vs non-squamous) and smoking status (never vs former/current).

For baseline and Week 48, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report[32]

Figure 7. Empirical Mean Change from Baseline and 95% CI for the EQ-5D VAS Over Time by Treatment Group (Observed Data Only) – PD-L1 TPS < 50% Subpopulation (PRO FAS Population; reproduced from CS Figure 7)

Source: Data on File. KEYNOTE-091 IA3 Statistical Report[32]

The company reports that in the current CS, EQ-5D utility scores were calculated using the UK EQ-5D-3L algorithm and value set. Analysis of the EQ-5D-3L utility score at Week 48 showed no clinically meaningful changes from baseline in either treatment groups. At Week 48, there was a difference in LS means of the EQ-5D-3L Utility Score of [redacted] (95% CI: [redacted]). Results are summarised in Table 24.

Utility scores used in the economic model were based on pooled data from both trial arms and controlled for the exclusion of adverse events. See Section 4.2.6.1 for further details.

Table 24. Analysis of Change from Baseline in EQ-5D-3L Utility Score to Week 48 Based on the United Kingdom Algorithm – PD-L1 TPS < 50% Subpopulation (PRO FAS Population; reproduced from CS Table 25)

	Baseline		Week 48		Change from Baseline to Week 48		
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) †	
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Pairwise Comparison					Difference in LS Means† (95% CI)		p-Value†

Pembrolizumab vs. Placebo	[redacted]	[redacted]

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment, stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous) and smoking status (never vs. former/current).

For baseline and Week 48, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Database Cutoff Date: 24JAN2023

Source: Data on File. KEYNOTE-091 IA3 Statistical Report[32]

3.3.5 Time on treatment

Time on treatment (ToT), the proportion of patients remaining on adjuvant pembrolizumab at each scheduled infusion was also used in the company's economic model. This was based on the observed Kaplan-Meier curve for time to treatment discontinuation in the KEYNOTE-091 trial. As discussed in Section 2.3.2, patients randomised to adjuvant pembrolizumab received treatment for a maximum of 18 doses (approximately 1 year). As a result, a small percentage of patients in the pembrolizumab group remained on treatment beyond 1 year, but no patients received more than 18 doses. See Section 4.2.7 for further discussion on the use of ToT.

3.3.6 Safety

In the CS, AEs observed were presented for the Prior Adjuvant Chemotherapy population and for the Overall Population, as data for the PD-L1 TPS <50% subpopulation were not available, and the company reported that no substantial differences in the safety profile were expected between the two populations. The EAG's clinical experts confirmed that the safety profile of participants with PD-L1 TPS <50% is not likely to differ from patients with prior adjuvant chemotherapy and higher PD-L1 TPS expression. A summary of AEs associated with pembrolizumab from the KEYNOTE-091 trial observed as of IA3 (data cut-off date of 24-JAN-2023) is provided below.

As stated in Section 3.2, the APaT population consisting of all randomised participants who received at least one dose of study treatment was used for the safety analysis. This was applicable to both the prior adjuvant chemotherapy population (licensed population) and the Overall Population. The EAG notes that the rates of the all-cause grade 3+ AEs that occurred with a frequency of ≥1% in any of the KEYNOTE-091 arms in the Overall Population (APaT) were used in the company's economic model. As discussed further in Section 4.2.6.3, the mean duration per AE episode, the mean number of episodes per patient with each included AE and the percent of AEs resulting in hospitalisations were used in the economic model. These are presented in Table 26 below. Relevant data presented in the clinical section of the CS were on participants with Grade 3-5 AEs by decreasing incidence (incidence ≥1%) in the Overall Population (APaT). These are presented in Table 25 below.

There were 1,085/1,161 participants in the Overall Population (APaT) experiencing an adverse event. The proportion of patients experiencing an AE in each group was 95.9% and 91% for pembrolizumab group and placebo, respectively. There were 348/1,161 (approximately 30%) participants in the Overall Population (APaT) that experienced a Grade 3-5 AE. The percentage of participants with Grade 3-5 AEs was greater in the pembrolizumab group (34.1%) compared to placebo (25.8%). The

most frequently reported (≥2% incidence) Grade 3 to 5 AEs in one or more treatment groups were hypertension ([redacted]) and pneumonia ([redacted]). The percentage of participants with drug-related Grade 3 to 5 AEs was greater in the pembrolizumab group compared to the placebo group (15.3% vs 4.3%).

The EAG notes that overall, there were 17 deaths reported up to 90 days from the last study dose, 11 (1.9%) in the pembrolizumab group and 6 (1.0%) in the placebo group. [redacted] of the deaths in pembrolizumab and [redacted] of the deaths in the placebo group were due to AEs considered to be drug-related by the investigator (myocarditis [redacted], cardiogenic shock [redacted], pneumonia [redacted], septic shock [redacted] and sudden death [redacted]).

Table 25. Participants with Grade 3-5 Adverse events by Decreasing Incidence (Incidence ≥1%; reproduced from CS, Table 31)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	580		581	
with one or more adverse events	198	(34.1)	150	(25.8)
with no adverse events	382	(65.9)	431	(74.2)
Hypertension	[redacted]		[redacted]	
Pneumonia	[redacted]		[redacted]	
Diarrhoea	[redacted]		[redacted]	
Dyspnoea	[redacted]		[redacted]	
Hyponatraemia	[redacted]		[redacted]	
Pneumonitis	[redacted]		[redacted]	
Weight increased	[redacted]		[redacted]	

	[redacted]	[redacted]	[redacted]
Every participant is counted a single time for each applicable specific adverse event. A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. Non-serious adverse events up to 30 days of last dose, serious adverse events up to 90 days of last dose and Adverse Events of Special Interest (AEOSI) up to 90 days of last dose are included. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. NCI CTCAE version 4.03 Database Cutoff Date: 24JAN2023			

Source: Data on File. KEYNOTE-091 IA3 Clinical Study report [33]

Table 26. Adverse event incidence and duration (all cause grade 3+; reproduced from CS, Table 49)

AE type	AE risk (%), by adjuvant treatment arm		Mean number of episodes per patient with AE	Mean duration of AE per episode (weeks)	% of AE episodes resulting in hospitalisation
	Pembrolizumab	Placebo			
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AE, adverse events					

The EAG's clinical experts agreed that the safety profile observed for participants treated with pembrolizumab was largely consistent with the known safety profile of pembrolizumab. However, they noted that although consistent, the safety profile did not capture all of the AEs expected to commonly occur with pembrolizumab such as hyperthyroidism, nephritis and hepatitis. The EAG's clinical experts also noted the rate of diarrhoea was lower than expected in clinical practice in England and highlighted those patients in whom diarrhoea results in hospitalisation, would require admission to outpatients for further testing or treatment. EAG clinical experts also noted that the rate of hospitalisation for pneumonitis may be higher in clinical practice than captured in the trial, although patients would be expected to be discharged quickly, after being treated with steroids and antibiotics.

In the CS, the company provided the mean number of episodes per patient with AE, mean duration of AE episode and the rate of AE episodes resulting in hospitalisation for all patients (APaT population) irrespective of treatment arm, as used in the economic model (Table 26). The EAG noted

that these may differ between treatment arms, considering that patients in the placebo arm are not given active treatment and requested that the company provides this data by treatment arm. In response to the EAG's clarification question, the company provided the data separately by treatment arm. These are shown in Table 27 and Table 28 below. The EAG notes that for the majority of AEs, the mean duration and the proportion hospitalised was higher in the pembrolizumab group.

Table 27. Adverse event incident and duration for pembrolizumab (all cause grade 3+; reproduced from Table 27 in the company's clarification response)

AE type	Pembrolizumab			
	AE risk (%)	Mean number of episodes per patient with AE	Mean duration of AE per episode (weeks)	% of AE episodes resulting in hospitalisation
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse events

Table 28. Adverse event incident and duration for placebo (all cause grade 3+; reproduced from Table 28 in the company's clarification response)

AE type	Placebo			
	AE risk (%)	Mean number of episodes per patient with AE	Mean duration of AE per episode (weeks)	% of AE episodes resulting in hospitalisation
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]

Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: AE, adverse events				

3.4 Critique of the indirect comparison and/or multiple treatment comparison

As KEYNOTE-091 trial, identified in the company's SLR, provided direct comparative evidence on the clinical effectiveness of pembrolizumab overactive monitoring, the comparator deemed relevant for this appraisal, in the patient population of interest (PD-L1 TPS <50% subpopulation), no indirect or mixed treatment comparisons were conducted.

3.5 Conclusions of the clinical effectiveness section

The EAG considers the key evidence submitted by the company in support of the clinical efficacy and safety of pembrolizumab for adjuvant treatment of resected NSCLC to be from the Prior Adjuvant Chemotherapy PD-L1 TPS <50% subpopulation (n=726) of the KEYNOTE-091 trial.[25, 26] KEYNOTE-091 (NCT02504372) was a randomised, triple-blinded, placebo-controlled, multicentre trial evaluating the efficacy and safety of adjuvant pembrolizumab versus placebo in participants with Stage IB (T2a ≥ 4cm), II or IIIA (AJCC 7th edition) NSCLC who have undergone complete resection followed by standard adjuvant chemotherapy (where appropriate as per relevant local guidelines).

The NICE final scope describes the population of interest for pembrolizumab as adults with NSCLC who have undergone complete surgical resection with or without adjuvant chemotherapy. Pembrolizumab has MA as adjuvant treatment for adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy, thus the EAG considers the company's choice to address adults with NSCLC who have undergone complete surgical resection with adjuvant chemotherapy in the decision problem reasonable and in line with MA for pembrolizumab.[19] However, the EAG notes the company's choice to only cover the subpopulation whose tumours express PD-L1 TPS with less than 50% TPS in the current submission is not aligned with the MA for pembrolizumab. The EAG considers PD-L1 TPS <50% subpopulation to align well with the NICE final scope in terms of intervention and outcomes but considers the choice to focus on this subpopulation *post-hoc* to potentially be data-driven and hence at high risk of bias.

Based on clinical expert advice, the EAG considers the baseline characteristics of the KEYNOTE-091 PD-L1 TPS <50% subpopulation to be representative of adults with NSCLC who are at high risk of recurrence following complete resection and platinum-based chemotherapy in clinical practice in England with some potential discrepancies, the most important of which is age. Based on data available on the mean age at diagnosis of all patients with NSCLC in England in 2012 who received surgery, the EAG considers the average age of participants in the PD-L1 TPS <50% subpopulation of the KEYNOTE-091 trial to be younger than patients with NSCLC expected to be eligible for pembrolizumab in clinical practice in England. The EAG has concerns over the representativeness of the age of participants in the KEYNOTE-091 trial for clinical practice in England and the potential impact of this on clinical effectiveness results and particularly on overall survival, specifically:

- background mortality is expected to increase with age;
- any utility benefit associated with an overall survival benefit due to pembrolizumab is expected to decrease with increasing age;
- the EAG's clinical experts anticipate that a higher cure rate will be achieved with pembrolizumab in a younger population compared to an older population.

The EAG noted that in the PD-L1 TPS <50% subpopulation, pembrolizumab showed a significant reduction in the risk of disease recurrence or death compared to placebo; however, there was uncertainty regarding OS. The median follow-up was [redacted] months in the pembrolizumab group and [redacted] months in the placebo group and at interim analysis 3 with a database cut-off date of 24-JAN-2023, 84 (23.1%) people in the pembrolizumab group and 110 (30.3%) people in the placebo group had died. Thus, the EAG notes the OS estimate was immature and more mature survival analysis data are needed to give a more accurate estimate of OS.

4 Cost effectiveness

Table 29 below presents the incremental cost-effectiveness results of the company's updated (i.e., post clarification) base case. Results presented in this document are inclusive of a [redacted] patient access scheme (PAS) discount for pembrolizumab. The company's base case analysis compared pembrolizumab to placebo.

Table 29. Company's base case results post clarification, PAS included

Intervention	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,106
Probabilistic results							
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,148

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

4.1 EAG comment on the company's review of cost effectiveness evidence

The company conducted a single systematic literature review (SLR) to identify cost effectiveness, health-related quality of life (HRQoL) and resource use and cost for adjuvant therapy in early-stage non-small cell lung cancer (NSCLC). Searches were initially run in August 2021, with an update performed in March 2022 and were last updated in October 2023. A summary of the External Assessment Group's (EAG's) critique of the methods implemented by the company to identify relevant evidence is presented in Table 30.

Table 30. EAG's critique of company's systematic literature review

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G	Appendix G	Appendix G	Appropriate
Inclusion/ exclusion criteria	Appendix G	Appendix G	Appendix G	Appropriate
Screening	Appendix G	Appendix G	Appendix G	Appropriate
Data extraction	Appendix G	Appendix G	Appendix G	Appropriate
Quality assessment of included studies	Appendix G	Appendix H	Appendix I	Appropriate

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health related quality of life.

In total (original search, March 2022 update and October 2023 update), the SLR identified a total of 2,514 records, with 259 selected for full text screening. Forty-seven publications were selected for final inclusion, with 30 publications relevant for the cost-effectiveness evidence, 16 publications related to resource use and costs and 1 utility study. Appendix G, Section B.1.1 of the CS describes the economic evaluations identified by the SLR, Appendix H presents the resource use and cost evidence and Appendix I describes the utility study identified by the SLR.

Overall, the EAG considers the company's SLR was thorough and comprehensive. The EAG is satisfied that the relevant evidence for this topic, specifically the NICE technology appraisals (TAs) and Scottish Medicine Consortium (SMC) guidance for atezolizumab (TA823 and SMC2492)[34, 35] and osimertinib (TA761 and SMC2383),[36, 37] as well as NICE guidelines for lung cancer (NG122)[38] were identified by the SLR and were used by the company to inform the development of their *de novo* cost-effectiveness model.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 31 summarises the EAG's assessment, of the company's economic evaluation, against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.3.

Table 31. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Appropriate.
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective
Type of economic evaluation	Cost–utility analysis	Appropriate
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime (36 years)
Synthesis of evidence on health effects	Based on systematic review	The company performed an appropriate systematic review

Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	All values for HRQoL were taken from KEYNOTE-091 using EQ-5D-3L measures
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-3L data reported directly from patients in the KEYNOTE-091 trial
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Patients in KEYNOTE-091 were considered mostly representative of the UK population. Age has been identified as underestimated. See section 2.3.1 and 4.2.2.1
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The economic evaluation matches the reference case
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	All relevant costs appear to be included appropriately
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate of 3.5% has been used for both costs and health effects

Abbreviations: EAG, External Assessment Group; EQ-5D, EuroQol 5 dimension; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2 Population

The population used in the economic model differs from the NICE final scope for pembrolizumab, as discussed in Section 2.3.1. This submission focuses on adults with NSCLC who have undergone complete surgical resection after adjuvant platinum-based chemotherapy and whose tumours have PD-L1 TPS <50%. A narrower population was used to focus on those who would likely receive the greatest benefit from treatment.

Baseline patient data, from the KEYNOTE-091 trial, used in the model is summarised in Table 32. In addition a GFR (glomerular filtration rate) of 75.0 ml/min/1.73m^2 was assumed based on NICE TA181.[39] The value was back calculated based on the Calvert formula for carboplatin dosing:

Total Dose (mg) = (target AUC) x (GFR + 25)

500mg = 5 x (GFR + 25)

75 ml/min/1.73m^2 = GFR

For baseline characteristics the overall population (ITT population) was used, which included patients without prior adjuvant platinum-based chemotherapy and patients whose tumours have PD-L1 TPS ≥50%.

Table 32. Baseline characteristics of the population used in the cost-effectiveness analysis (based on table 35 of the CS)

Characteristic	Overall	SE
Starting age (years), mean	64.3 years	NR
Percentage female (percentage)	31.7%	NR
Body surface area (m^2), mean	1.9	0.01
Weight (kg), mean	74.8	0.5
Abbreviations: kg, kilograms; m^2, metres squared; NR, not recorded; SE, standard error.		

Age and percent female impacts the time horizon of the model along with the general population related mortality/utility values applied to patients.

Body surface area affects dosing of docetaxel, cisplatin, paclitaxel/nab-paclitaxel and pemetrexed. GFR affects the dose given of carboplatin. Details on the market share of these treatments and the impact of body surface area and GFR on dosing is found in section 4.2.7.1.

Weight has no impact in the base case but has the potential to impact dosing of bevacizumab, ipilimumab and ramucirumab if these treatments were to be incorporated into subsequent treatment use.

4.2.2.1 EAG critique

The company used the ITT population of KEYNOTE-091 to inform the baseline characteristics in the model despite using a narrower target population to inform effectiveness. At clarification, a scenario using the baseline characteristics of only the target population of adults with NSCLC who have undergone complete surgical resection after adjuvant platinum-based chemotherapy and whose tumours have PD-L1 TPS <50%, was requested. The characteristics of this population are listed in Table 33. While the characteristics of both populations appear to be similar, the EAG believes the PD-L1 TPS <50% population should be used as the base case, given it makes up the target population for this appraisal. Furthermore, the company did not incorporate a standard error for starting age or percentage female into the model and therefore did not vary these values in the PSA. These values should be varied in the sensitivity analysis as there is uncertainty as to whether they accurately represent clinical practice. The EAG has updated the model to accommodate for these two issues. These two issues make up **additional issue 1** and **additional issue 2** referenced in section 1.5.

Table 33. Baseline characteristics of the PD-L1 TPS <50% subpopulation used in the EAG base case cost-effectiveness analysis

Characteristic	Overall	SE
Starting age (years), mean	[redacted] years	[redacted]
Percentage female (percentage)	[redacted] %	[redacted]
Body surface area (m^2), mean	[redacted]	[redacted]
Weight (kg), mean	[redacted]	[redacted]
Abbreviations: kg, kilograms; m^2, metres squared; SE, standard error.		

As noted in section 3.2 participants in the KEYNOTE-091 trial were identified, by clinical experts, as being younger than patients in clinical practice in England. This is supported by the SEER-Medicare cohort baseline age at surgery being 73.5,[40] although, it is notable that Medicare has a minimum age of 65.

The company stated at CQ that removing all patients aged under 65 from a normally distributed cohort, with mean [redacted] and SD=[redacted] years, as in the PD-L1<50% group in KEYNOTE-091, results in a residual mean of 71 years. Although, this estimate is notably lower than that recorded in SEER-Medicare and age is unlikely to be normally distributed, as it is a significant risk factor for NSCLC and so, ceteris paribus, you would expect a higher number of people having the disease with increasing age. In addition, the company identified that previous trials for NSCLC patients had a similar or lower median age for patients[41-43], yet this would be expected as it is common for clinical trials to select a younger cohort than the general patient population.

At clarification the company was asked to source data from UK clinical practice. The company was able to identify 4 studies but stated that these were only single-centre. The company did not elaborate on the contents of these studies beyond referencing them in the statement that, "A number of studies have shown a lower median age for patients". When investigating the contents of these studies, only one (Jessica *et al.* 2024[44]) appeared to have a lower median age of 62; all other studies cited had median ages of 70. The EAG identified 2 additional UK based studies, one was a single-centre study,[45] similar to those found by the company, the other uses the total national cancer registry for England.[46] All studies along with the median ages are shown in Table 34. The results of this table appear to validate the claim that the current baseline age is underestimated. The EAG base case preference is to use the baseline age of 68.4[46]. The EAG has also applied the SEER-Medicare age as a conservative scenario on the company base case. This is **Key issue 2** referenced in section 1.1.

Table 34. UK-specific evidence on age distribution

Trial name	Median Age (range), years
KEYNOTE-091[a] (adjuvant)	[redacted]
Jessica *et al*. 2024[b]	62 (42 to 74)
Ugolini *et al*. 2023[c]	70 (45 to 81)
Escriu *et al*. 2023[d]	70 (44 to 92)
Trevelyan *et al*. 2024[e]	70 (not reported?)
Belcher *et al*. 2021[f]	70.4 (18.1 to 87.7)
Belot *et al*. 2019[g]	68.4 (mean)

[a] Median is reported for all patients in the PD-L1 TPS <50% Subpopulation

[b] Median is reported for 50 patients with resected stage 2 and 3 NSCLC in Bristol

[c] Median is reported for 58 patients who underwent surgical resection in Manchester

[d] Median is reported for 134 resectable early-stage NSCLC UK patients

[e] Median is reported for 321 NSCLC patients who underwent curative treatment with surgery in Plymouth

[f] Median is reported for 467 operative patients treated in Oxford

[g] Median is reported for 4850 NSCLC patients who received surgery in England

4.2.3 *Intervention and comparator*

Pembrolizumab (KEYTRUDA®) is a monoclonal antibody that binds to the PD-L1 receptor, potentiating an immune response to tumour cells. The intervention is available as 25 mg/mL concentrate solution for infusion and the recommended dose is either 200 mg Q3W or 400 mg Q6W administered as an intravenous infusion over 30 minutes.[20] The company base case used Q3W dosing while Q6W was provided as a scenario analysis.

The company considered active monitoring to be the only relevant comparator for pembrolizumab. This effectively means there is no additional cost to the treatment of disease-free patients in the comparator arm that is not also applied to the intervention arm.

4.2.3.1 *EAG critique*

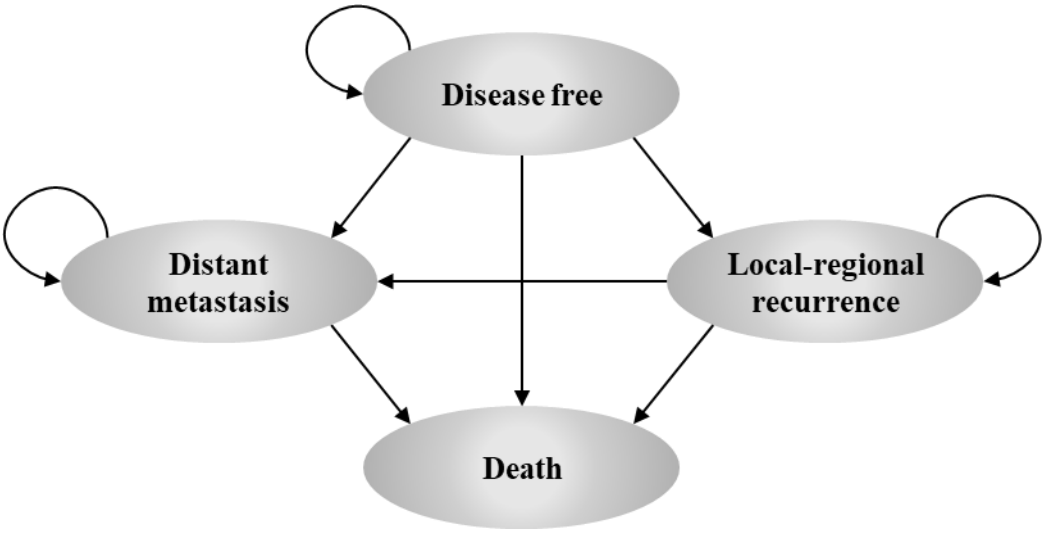
Clinical experts advised the EAG that Q6W would likely be more commonly used in clinical practice for both adjuvant and metastatic treatment of pembrolizumab. At clarification, the company suggested clinicians prefer to monitor patients more closely in the metastatic setting and therefore will tend to prefer Q3W. However, no evidence was presented for this and the company acknowledged both adjuvant and metastatic would likely have a mix of both in clinical practice. The EAG requested guidance from NHS England on this topic, who advised that patients would start on 3-weekly before transitioning to 6-weekly after 2-3 months, provided no toxicity was observed. Since

the intervention is adjuvant, NHSE stated there would be less concern about monitoring patients. There are capacity issues in chemotherapy units at present so it is expected that most patients will receive pembrolizumab 6-weekly. Based on this information the EAG have assumed Q6W to represent 75% of administrations of pembrolizumab in the base case (assuming transition to Q6W after 3 months). To maintain consistency the same rate is applied to pembrolizumab treatment administered as a subsequent therapy. This is **additional issue 3** referenced in section 1.5.

4.2.4 Modelling approach and model structure

The company produced a cohort-level Markov state transition model programmed in Microsoft Excel,® comprising of four health states: "disease free", "local-regional recurrence", "distant metastasis" and "death" (see Figure 8). Within the "distant metastasis" health state there were two sub-states as patients could experience first or second line treatments. The model uses a lifetime time horizon with a weekly cycle length based on the primary endpoint of the KEYNOTE-091 Phase 3 trial (disease free survival), with a half-cycle correction applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.

Figure 8. Model schematic



While the model is a Markov state transition model, it shares features with partitioned survival models, more commonly used for NICE cancer appraisals. Transition probabilities vary over time using parametric functions based on real-world data.

The transition probability of patients moving from disease-free survival is determined by data from the KEYNOTE-091 trial,[33] with death determined by national life tables.[47] SEER-Medicare cohort

data[40] were used for local-recurrence transitions, with this being further adjusted to match OS outcomes from KEYNOTE-091. For distant metastases data from KEYNOTE 189 and 407[48, 49] was used alongside the SEER-Medicare database. Further details are included in section 4.2.5.

4.2.5 Treatment effectiveness

As stated in the prior section, transitions were variable and based on modelling assumptions applied to real-world data. The primary driver of differences in effectiveness between the intervention and comparator was the DFS transitions, yet the company also assumed differences in mortality and progression, would persist between the two arms, even following recurrence.

4.2.5.1 Disease-free survival

Different parametric functions were fitted to each of the three individual transitions from disease-free survival. All disease free survival transition rates were determined by data taken from the patients who had received adjuvant platinum-based chemotherapy and had PD-L1 TPS <50% population of KEYNOTE-091.[33]

To model each of the three transition rates to: local recurrence, distant metastatic recurrence and death, other failure types were treated as censoring events. In the base case individual parametric models were applied to each transition state and each treatment arm. Models were selected based on the following criteria:

- Visual assessment of fit vs observed DFS to event curves.
- Mean squared errors (MSE) was used to estimate prediction error. The company stated Akaike Information Criterion (AIC) was used; Bayesian information criterion (BIC) was not referenced. The MSE recorded by the company was for modelling overall DFS versus observed DFS as opposed to individual MSE for each form of treatment failure model vs the observed rates of that specific failure.
- Assessment of modelled OS vs observed trial OS. The company stated that, while all models appeared to result in OS being underpredicted, ones which led to the greatest level of underprediction were excluded.
- Assessment of clinical plausibility of post-trial extrapolations.
- Used the same functional form in each arm and for each failure type in absence of strong evidence to the contrary.

Within the trace, parametric curves were applied in model using the formula:

$$1 - e^{-\overline{h}_{DFS}(t)} * \frac{\overline{h}_k(t)}{\overline{h}_{DFS}(t)}$$

Where $-\overline{h}_{DFS}(t)$ represents hazard for all cause DFS failure and $\overline{h}_k(t)$ represents hazard for a specific DFS failure. For transition to LR and DM the hazard was variable and for death the hazard was fixed or used general population mortality (whichever was higher).

The company provided the scenario analysis using alternative modelling approaches. The model contains an option to apply parametric proportional hazard models between the intervention and control arm. This would still involve separate models by failure type. Another option currently included in the model is proportional hazards models with piecewise fittings with a cut-point at 1 year; this being based on completion of adjuvant treatment with pembrolizumab. Both of these alternative approaches had a poorer fit compared to static hazard curves, individually fit to each treatment arm/treatment failure transition.

The top 10 combinations of individually fitted parametric curves, ranked by MSE, are shown in Table 35 for pembrolizumab and Table 36 for placebo.

Table 35. Comparison of different parametric functions used to model DFS in the pembrolizumab arm for patients who received adjuvant chemotherapy with PD-L1 TPS<50%: Fit with observed data and long-term extrapolations – parametric models fitted separately (taken from table 70 of the CS appendix)

Rank by MSE	Parametric functions		MSE vs. observed DFS	Predicted DFS (%)		Predicted OS (%)	
	DF → LR	DF → DM		Year 4	Year 5	Year 4	Year 5
1	Exponential	Log-normal	0.0001686	51	44	[redacted]	[redacted]
2	Weibull	Log-normal	0.0001734	50	44	[redacted]	[redacted]
3	Gompertz	Log-normal	0.0001742	50	44	[redacted]	[redacted]
4	Gamma	Log-normal	0.0001745	50	44	[redacted]	[redacted]
5	Log-logistic	Log-normal	0.0001783	50	44	[redacted]	[redacted]
6	Log-normal	Log-normal	0.0002097	51	45	[redacted]	[redacted]
7	Generalized gamma	Log-normal	0.0002306	51	45	[redacted]	[redacted]
8	Exponential	Log-logistic	0.0002717	50	43	[redacted]	[redacted]

9	Generalized gamma	Log-logistic	0.0002735	50	44	[redacted]	[redacted]
10	Generalized gamma	Weibull	0.0002758	50	43	[redacted]	[redacted]
Observed				51.2	42.9	[redacted]	[redacted]
Abbreviation: DF, disease-free; DFS, disease-free-survival; DM, distant metastatic recurrence; LR, local recurrence; OS, overall survival; MSE, mean square error.							

Table 36. Comparison of different parametric functions used to model DFS in the placebo arm for patients who received adjuvant chemotherapy with PD-L1 TPS<50%: Fit with observed data and long-term extrapolations – parametric models fitted separately (taken from table 73 of the CS appendix)

Rank by MSE	Parametric functions		MSE vs. observed DFS	Predicted DFS (%)		Predicted OS (%)	
	DF → LR	DF → DM		4	5	4	5
1	Generalized gamma	Gompertz	0.0001876	43	39	[redacted]	[redacted]
2	Generalized gamma	Log-normal	0.0003448	43	38	[redacted]	[redacted]
3	Generalized gamma	Generalized gamma	0.0003794	42	37	[redacted]	[redacted]
4	Generalized gamma	Log-logistic	0.0004084	42	37	[redacted]	[redacted]
5	Log-normal	Gompertz	0.0004084	42	37	[redacted]	[redacted]
6	Gompertz	Gompertz	0.0004290	43	39	[redacted]	[redacted]
7	Log-logistic	Gompertz	0.0004957	42	37	[redacted]	[redacted]
8	Generalized gamma	Weibull	0.0005426	42	36	[redacted]	[redacted]
9	Weibull	Gompertz	0.0005612	42	37	[redacted]	[redacted]
10	Gamma	Gompertz	0.0005865	42	37	[redacted]	[redacted]
Observed				42.4	39.2	[redacted]	[redacted]
Abbreviation: DF, disease-free; DFS, disease-free-survival; DM, distant metastatic recurrence; LR, local recurrence; OS, overall survival; MSE, mean square error.							

4.2.5.1.1 Disease-free survival to local recurrence

Log-normal was selected to model transition between disease-free and local-recurrence. The company noted that all parametric models for DF to LR fit reasonably well in both arms, as can be seen in Figure 9 and Figure 10. Log-normal was primarily preferred as it provided an appropriate fit

to both treatment groups (and due guidance in TSD14 about using the same model type in both arms unless there is strong evidence to the contrary).

At clarification the EAG requested the company list the fit statistics for individual competing risks. The AIC and log-likelihood for DF to LR parametric curves are found in Table 37.

Table 37. AIC and log likelihood statistics ranked best to worst fit, for locoregional recurrence risk curves from KEYNOTE-091 PD-L1<50% adjuvant chemo population

Distribution	Pembrolizumab		Placebo	
	Rank by loglik	Rank by AIC	Rank by loglik	Rank by AIC
exp	6	1	7	5
weibull	5	5	5	6
lnorm	2	2	2	2
llogis	7	7	4	4
gompertz	3	3	3	3
gengamma	1	6	1	1
gamma	4	4	6	7

Abbreviation: AIC, Akaike information criterion; DF, disease-free; DFS, disease-free-survival; loglik, log-likelihood.

The log-normal did not produce the obviously best fitting or lowest MSE curves for DF to LR in either arm but was the best fitting curve in the pembrolizumab arm for DF to DM. The company also stated, in reviewing DF to LR curves where DF to DM was assumed to be log-normal; Gompertz/log-normal and generalised gamma/log-normal curves should be excluded due to early convergence of DFS and OS and more severe underprediction of observed pembrolizumab OS. However, based on the results in Table 35, the OS at 5 years appears to be the same as log-normal/log-normal when rounded to the nearest whole number percentage.

Figure 9. Fit of all parametric models to DF to LR transition in pembrolizumab arm (figure 13 of CS appendix)

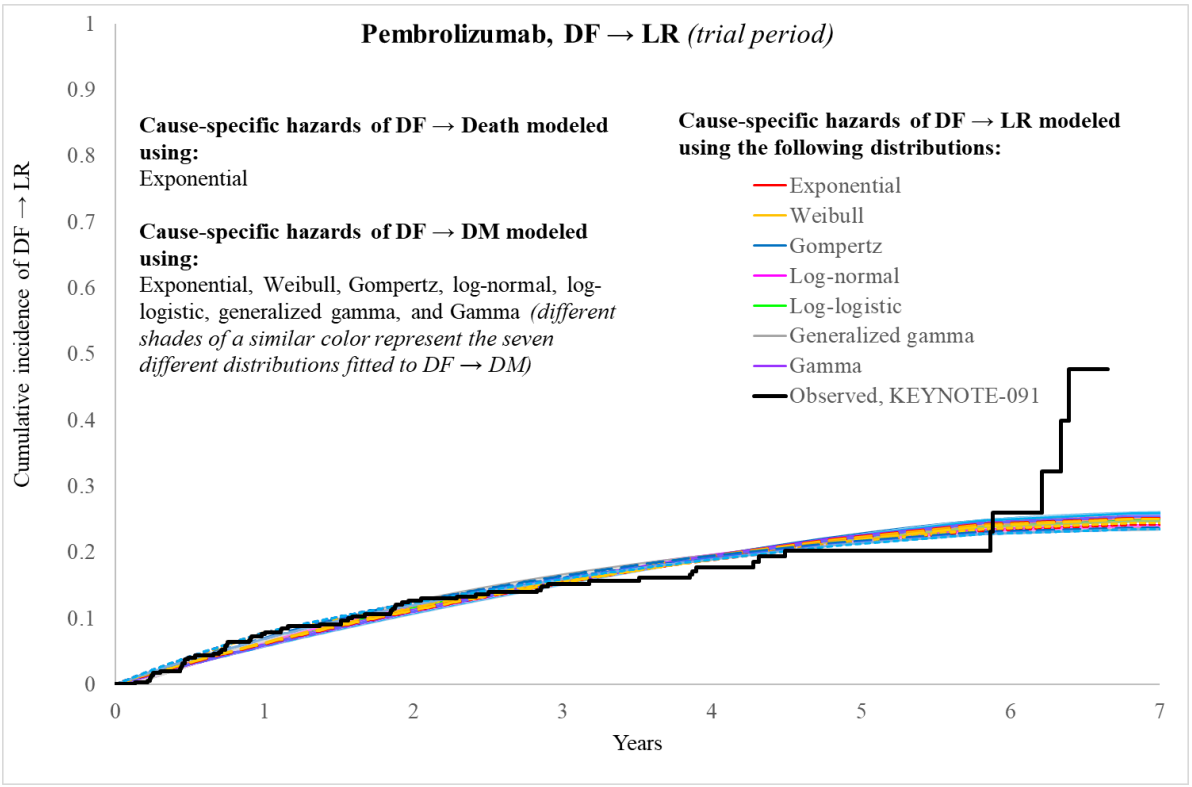
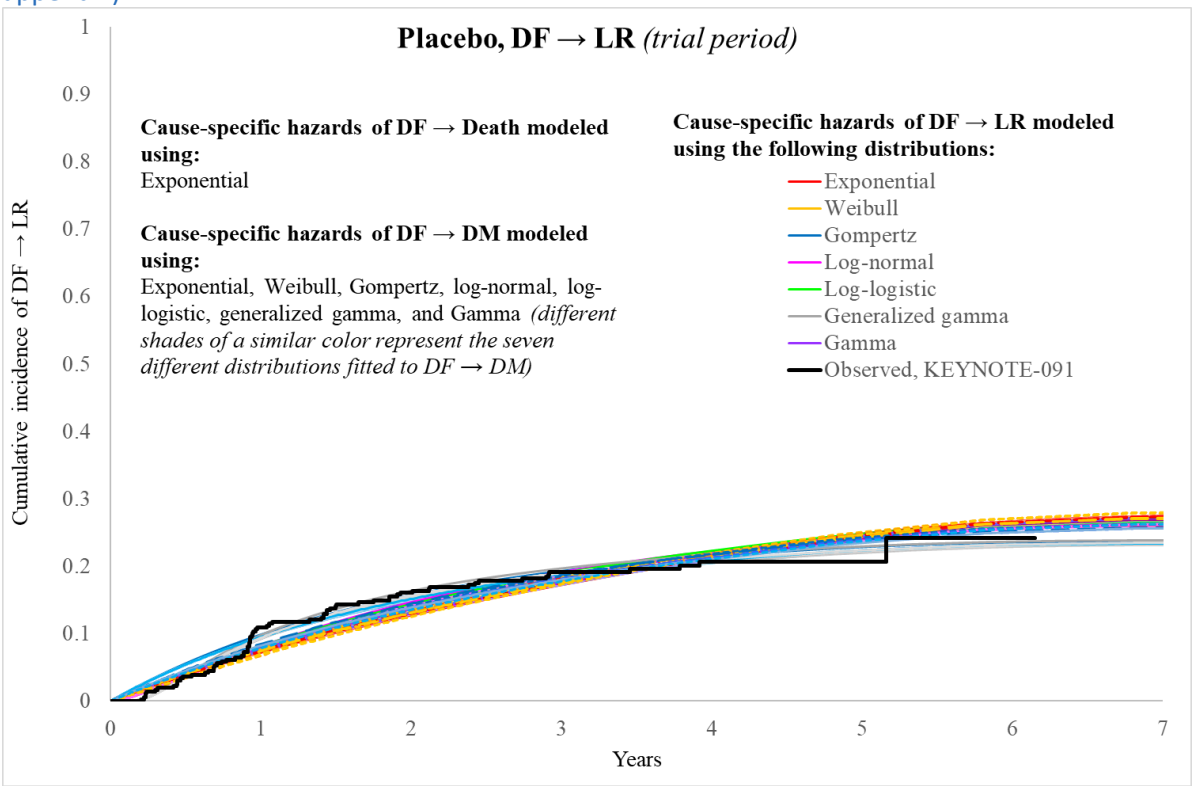


Figure 10. Fit of all parametric models to DF to LR transition in placebo arm (figure 14 of CS appendix)



4.2.5.1.2 Disease-free survival to distant metastatic recurrence

Among the individually selected parametric curve runs, for the pembrolizumab arm, the log-normal DF to DM produced the lowest 7 MSE scores (the lowest for every combination of DF to LR). In the placebo arm it produced the second lowest MSE scores but only when combined with generalised gamma. In both arms log-normal provided a clear fit, although in placebo Gompertz appeared to be a slightly better representation as seen in Figure 11 and Figure 12.

Gompertz was excluded as it resulted in zero hazards by 5-6 years, which was considered clinically implausible, leaving log-normal as the next best choice. For placebo, the Weibull, log-logistic and gamma curves first under then over predict cumulative incidence of DM, therefore these were excluded as options.

Figure 11. Fit of DF to DM parametric competing risks models in the pembrolizumab arm (copy of figure 15 of CS appendix)

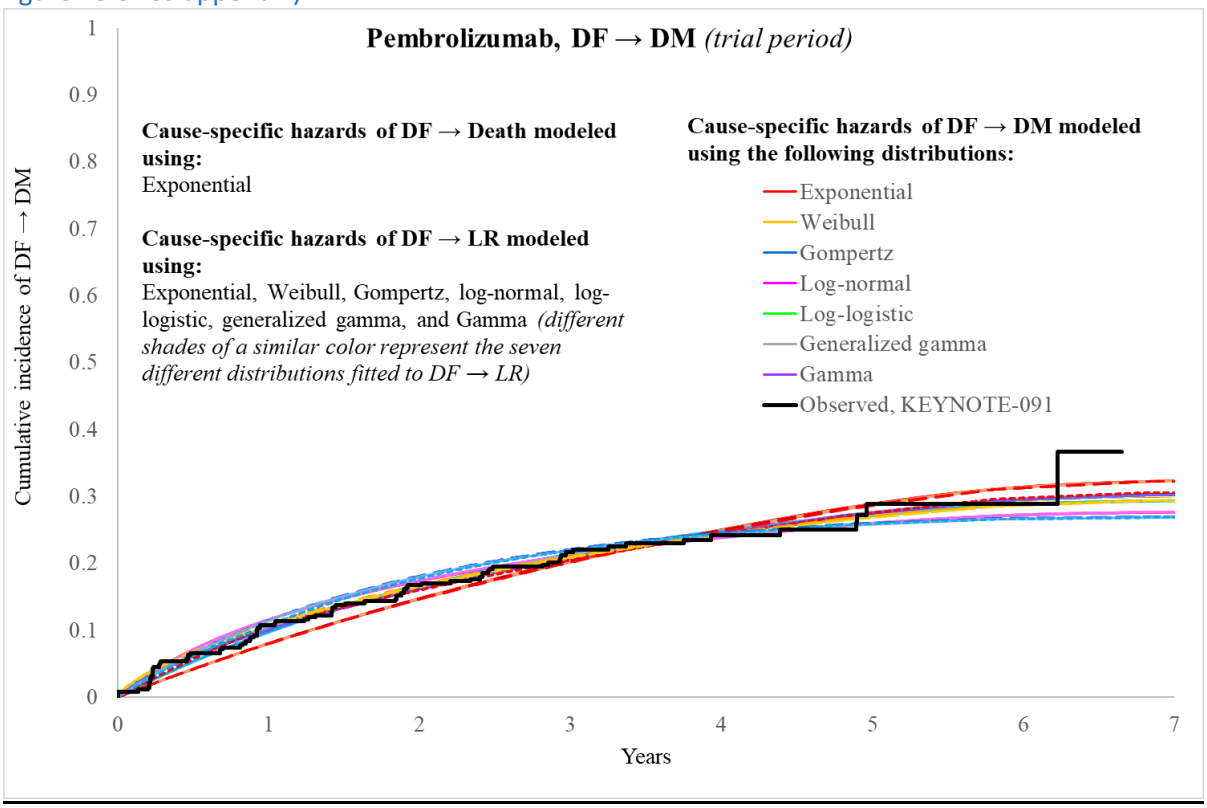
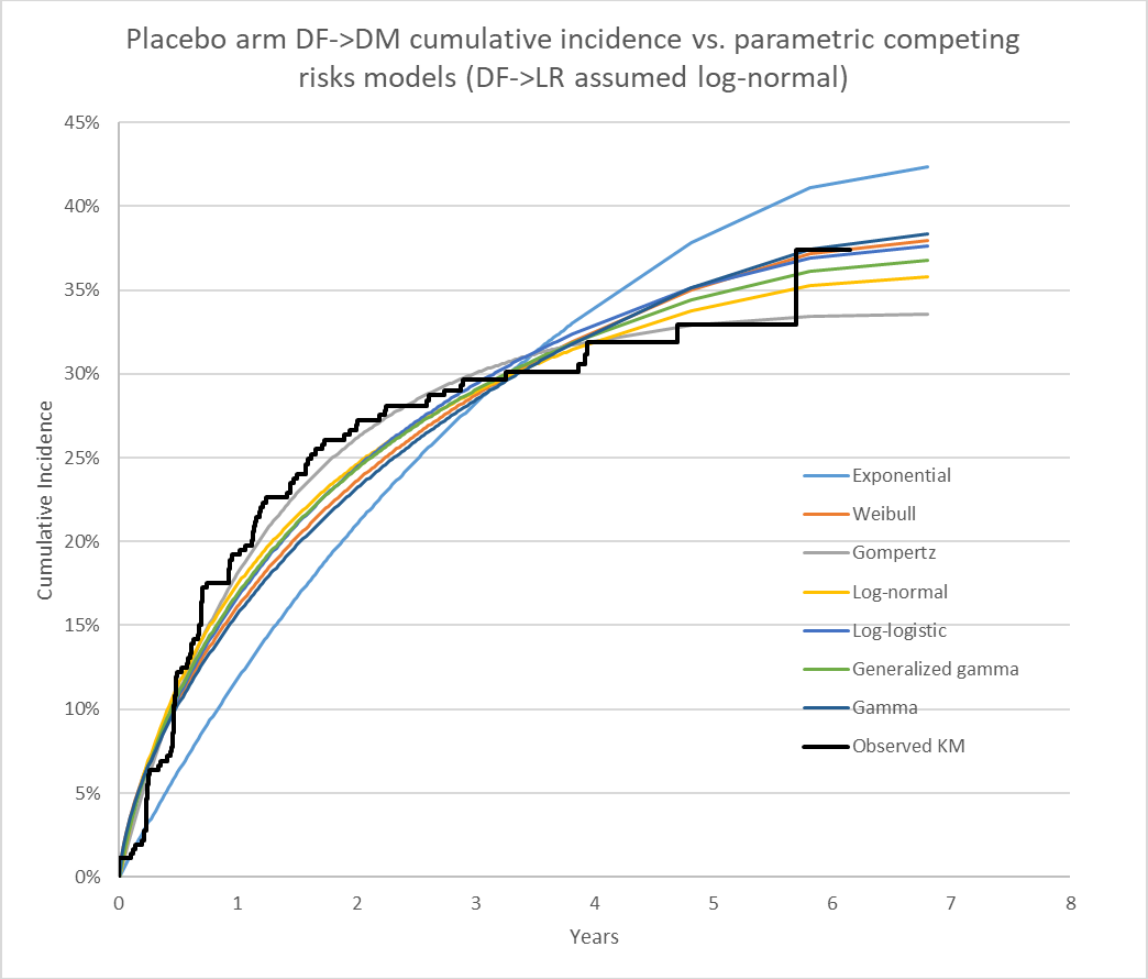


Figure 12. Fit of DF to DM parametric competing risks models in the placebo arm (copy of unnumbered figure in CS appendix)



At clarification the EAG requested the company list the fit statistics for individual competing risks.

The AIC and log-likelihood for DF to DM parametric curves are found in Table 38.

Table 38. AIC and log likelihood statistics ranked best to worst fit, for distant metastatic recurrence risk curves from KEYNOTE-091 PD-L1<50% adjuvant chemo population

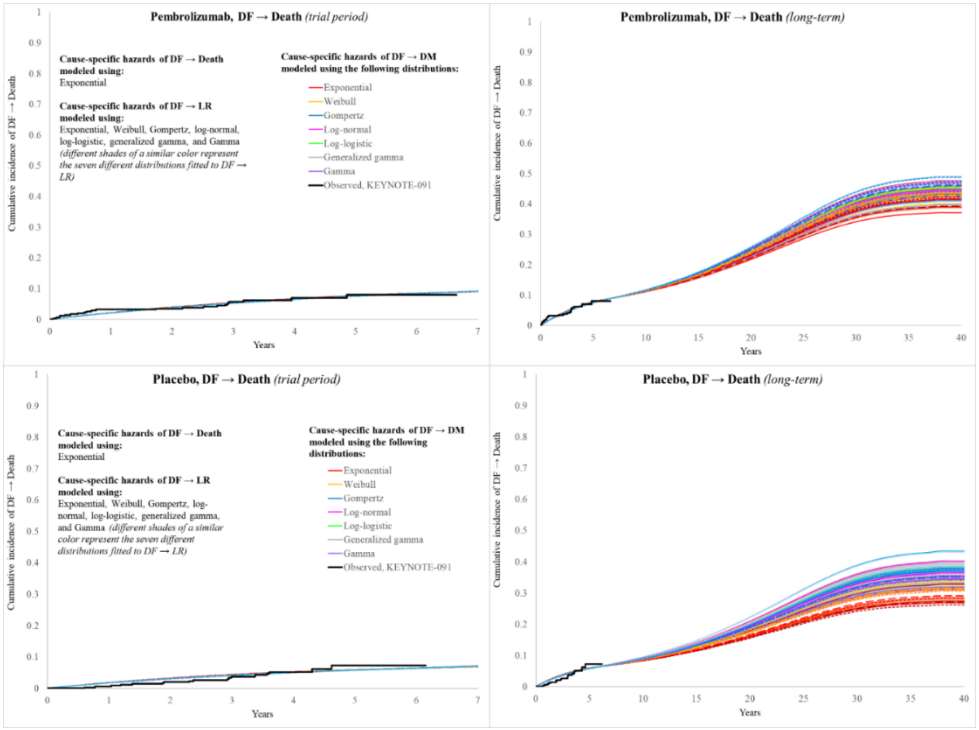
Distribution	Pembrolizumab		Placebo	
	Rank by loglik	Rank by AIC	Rank by loglik	Rank by AIC
exp	5	6	7	7
weibull	2	2	5	5
lnorm	6	7	4	3
llogis	3	3	2	2
gompertz	4	5	1	1
gengamma	1	4	3	4
gamma	1	1	6	6

Abbreviation: AIC, Akaike information criterion; DF, disease-free; DFS, disease-free-survival; loglik, log-likelihood.

4.2.5.1.3 Disease-free survival to death

Due to the small number of DF to death incidents observed, the transition rate was assumed to be exponential. Attempts to model the DF to death transition can be seen in Figure 13.

Figure 13. Predicted vs observed cumulative incidence of DF to death transitions in each arm among patients who received adjuvant chemotherapy with PD-L1 TPS<50%



At clarification the EAG requested the company list the fit statistics for individual competing risks. The AIC and log-likelihood for DF to Death parametric curves are found in Table 39. Notably exponential is the best fitting curve for pembrolizumab but the worst for placebo according to AIC. Although, differences between the highest and lowest scores was relatively small and, as can be observed in Figure 13, there is little difference in fit to the observed data between the different parametric curves.

Table 39. AIC and log likelihood statistics ranked best to worst fit, for locoregional recurrence risk curves from KEYNOTE-091 PD-L1<50% adjuvant chemo population

Distribution	Pembrolizumab		Placebo	
	Rank by loglik	Rank by AIC	Rank by loglik	Rank by AIC
exp	7	1	7	7
weibull	2	3	5	4
lnorm	5	5	2	1
llogis	4	4	4	3
gompertz	6	6	6	6
gengamma	3	7	1	5
gamma	1	2	3	2
Abbreviation: AIC, Akaike information criterion; DF, disease-free; DFS, disease-free-survival; loglik, log-likelihood.				

The mortality rate for patients in the disease free survival state is limited to at least occur at the general population mortality rate, as recorded in the 2020-22 ONS national life tables.[47] The final weekly exponential rates selected are shown in Table 40.

Table 40. Transition probabilities DFS to death

DFS to Death pembrolizumab		DFS to Death placebo	
Weekly exponential rate	SE	Weekly exponential rate	SE
0.00045	(0.00010)	0.00039	(0.0001)
Abbreviation: DFS, disease-free-survival; DM, distant metastases; NSCLC, non-small cell lung cancer; SE, standard error.			

4.2.5.1.4 Cure assumption

The base case model implements a cure point where the per-cycle risk of progression is linearly reduced up to 95%. This starts at year 5 and reaches 95% reduction by year 7 in order to avoid an immediate clinically implausible kink in reduction of recurrence. This approach mirrors one used in TA761.[36]

4.2.5.1.5 EAG critique

The difference in disease-free survival between placebo and adjuvant pembrolizumab provides an indication of the proportion of patients in which surgery with curative intent was not successful and adjuvant treatment has been beneficial. As such, for these disease-free patients, the treatment effect of adjuvant pembrolizumab may wane over time (i.e. the risk of recurrence in the DF health state for adjuvant pembrolizumab may decline over time to match placebo). As demonstrated in Table 62, there does appear to be some evidence of treatment waning from the observed DFS evidence. The treatment benefit from pembrolizumab consistently declines at every timepoint from 18 months.

Table 41. Summary of DFS Rate Over Time – PD-L1 TPS < 50% Subpopulation (ITT Population)

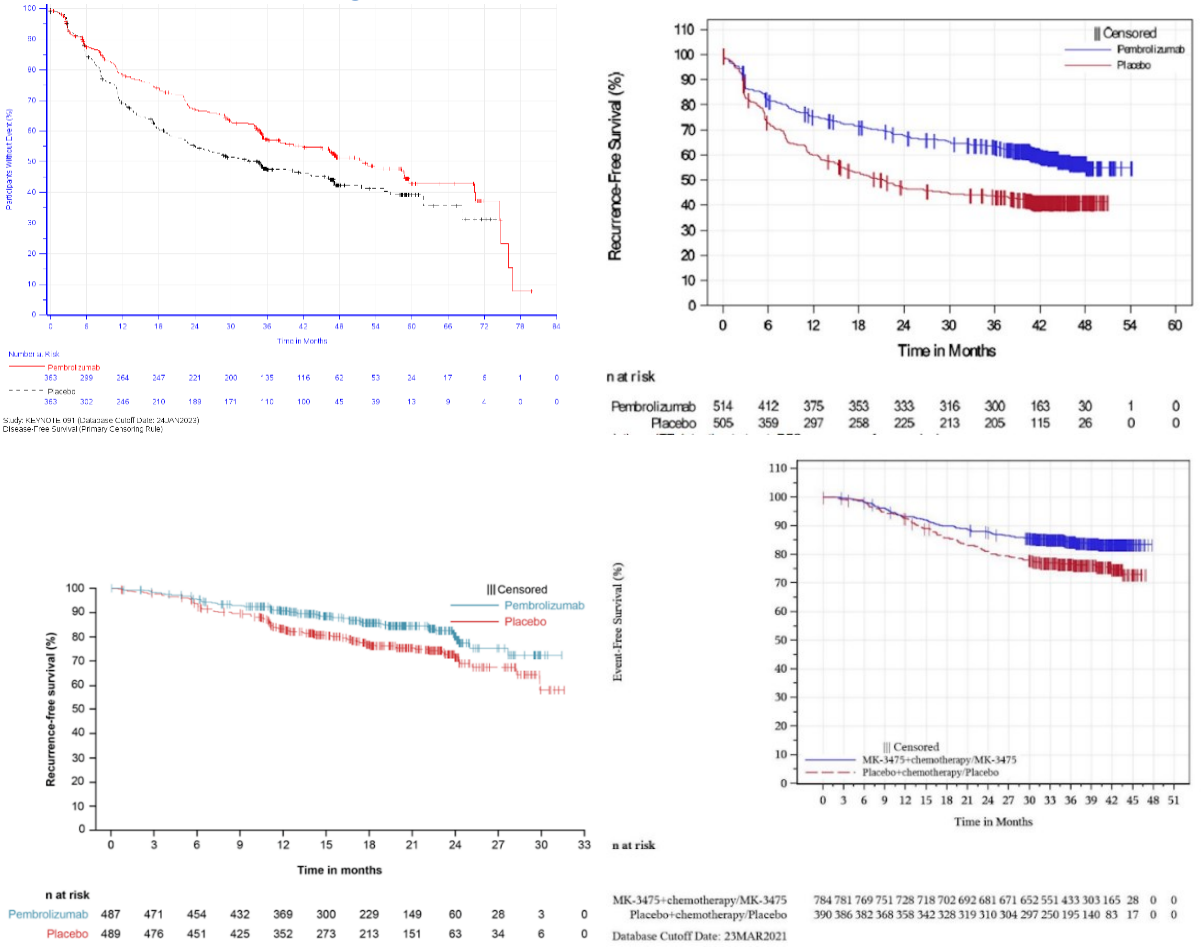
DFS rate (95% CI)	Pembrolizumab (N=363)	Placebo (N=363)	Difference
12 Months	[redacted]	[redacted]	[redacted]
18 Months	[redacted]	[redacted]	[redacted]
24 Months	[redacted]	[redacted]	[redacted]
30 Months	[redacted]	[redacted]	[redacted]
36 Months	[redacted]	[redacted]	[redacted]
42 Months	[redacted]	[redacted]	[redacted]
48 Months	[redacted]	[redacted]	[redacted]
54 Months	[redacted]	[redacted]	[redacted]
60 Months	[redacted]	[redacted]	[redacted]

Abbreviation: CI, confidence interval; DFS, disease-free-survival.

The EAG requested, at clarification, that the company provide a range of scenarios that test the impact on the ICER if the treatment effect of adjuvant pembrolizumab wanes over time and patients revert to the disease trajectory of patients on routine surveillance (convergence of DFS curves). The company did not provide this, noting that previous submissions involving use of adjuvant/neoadjuvant pembrolizumab treatment did not require this (TA766,[50] TA837[51] and TA851[52]). However, investigating the DFS data used to inform these submissions, only TA766 shows any sign of potential waning, and it is not as apparent as this submission. The KM data from these

submissions can be seen in Figure 14. In addition, in a recent appraisal for pembrolizumab for adjuvant treatment of renal cell carcinoma, the final guidance concluded that treatment waning should be incorporated into the pembrolizumab arm.[53]

Figure 14. Kaplan-Meier Estimates of Disease-Free Survival Top left this submission, top right TA766, bottom left TA837, bottom right TA851



The company also state that significant censoring of patients has happened by the point the waning appears to occur, with 33% of the DFS population and 40% of the OS population censored by 30 months and 48 months respectively. However, despite this censoring, the company considers there is still the data available at these timepoints to make extrapolations.

As a result of this evidence of waning, the EAG's position is that the proportional hazards assumption is potentially violated, and different curves may be reasonable for extrapolating pembrolizumab and placebo treatment arms. One attempt to address the waning issue involved requesting the company explore semi-parametric curves with a cut-point at 3 years. These did not outperform the individual

parametric curves approach selected for the EAG/company base case but did show a better fit than using the 1-year cut-point, as 3 year appears to be closer to where the treatment effect appears to begin to wane.

However, given the waning is visible within KM data, simply selecting different parametric curves for the treatments may be a reasonable way to account for this. While it is true that in the pembrolizumab arm all curves appear to fit equally well for DF to LR, in the placebo arm the generalized gamma appears to provide a far superior fit, which is further confirmed by the top 3 lowest MSE DFS combinations using generalized gamma in this arm. In addition, the EAG disagrees with the use of OS to justify excluding or including parametric curves for DFS. Fitting an appropriate curve for DFS should not be dependent on matching observed OS data based on post-recurrence assumptions. It should be solely about attempting to appropriately predict DFS based on the available observed DFS data.

Selecting for the best fitting curves according to the lowest MSE/AIC appears to better fit the KM data throughout the trial period. MSE and AIC only deviated in selecting the best fitting pembrolizumab curve for DF to DM, with the best fitting model according to MSE (log-normal) providing the worst fitting individual AIC statistic. Preference was given for the log-normal as it provided the best fit for the overall DFS data, even if the gamma curve had the lowest AIC and may have been the best fit for modelling DF to DM individually. The final selected models were exponential/log-normal for transition to LR/DM in pembrolizumab and a gen gamma/Gompertz for transition to LR/DM in placebo. The change is a minor improvement in fit for pembrolizumab but a significant improvement for placebo. Mean square error for the EAG in pembrolizumab was 0.0001686 versus 0.0002097 in the company model and in placebo it was 0.0001876 versus 0.0007512. The comparison between the EAG and company preferences can be seen in Figure 15 and Figure 16. A scenario was also conducted on the EAG base case in section 6.4, using the same curve assumptions but replacing the transition from DFS to LR from exponential to generalized gamma for pembrolizumab, since this had the best ranked log-likelihood and was also used to model DF to LR for placebo.

The EAG considers the improved fit from these preferences along with the observed treatment waning constitutes the strong evidence required for using different model types for each arm, as required by TSD14.[54] As this change may result in a significant knock-on impact on OS trajectory the calibration, referenced in section 4.2.5.3.1, was recalculated so it would be appropriate for the current modelled curves. This is **Key issue 3** referenced in section 1.1.

Figure 15. Disease-free survival EAG preferences

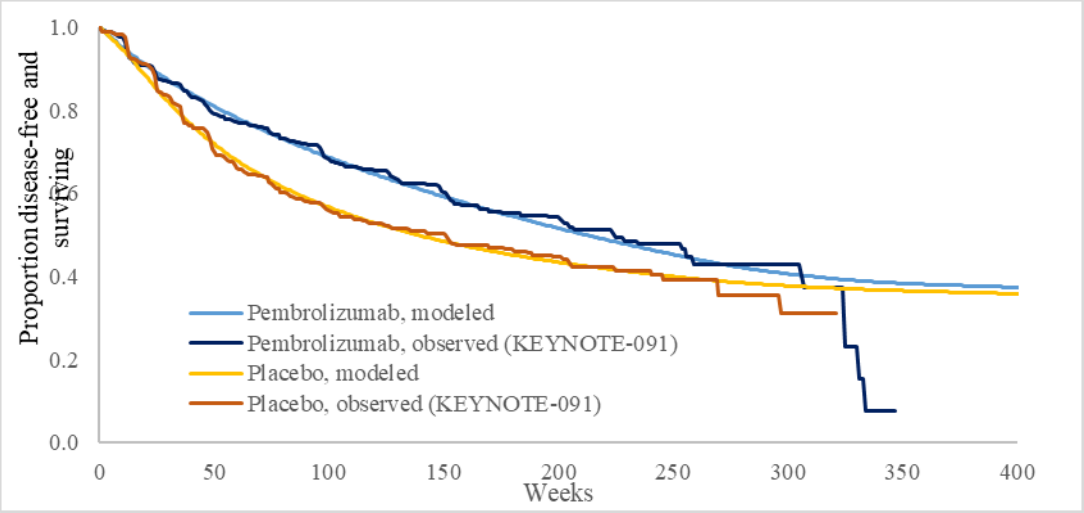
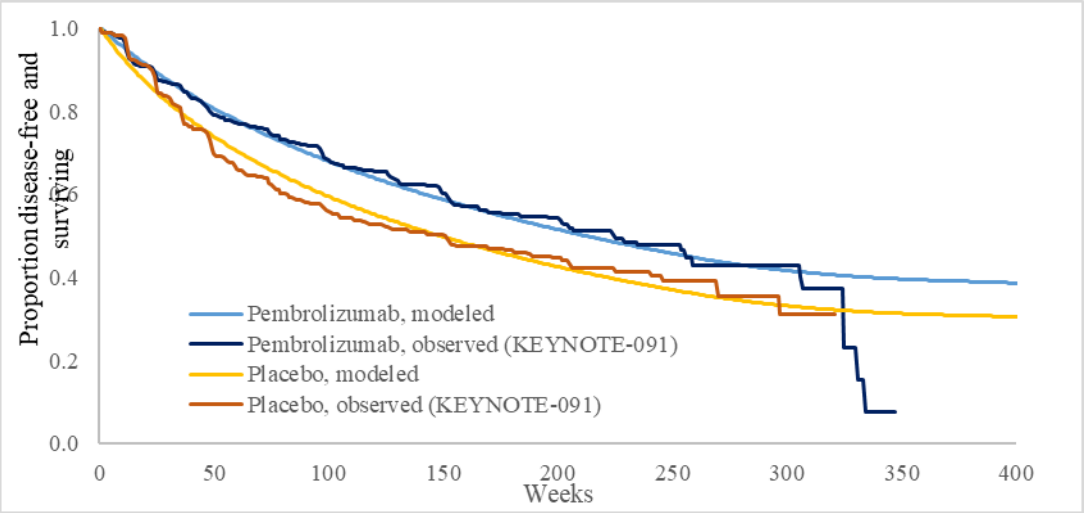


Figure 16. Disease-free survival company preferences

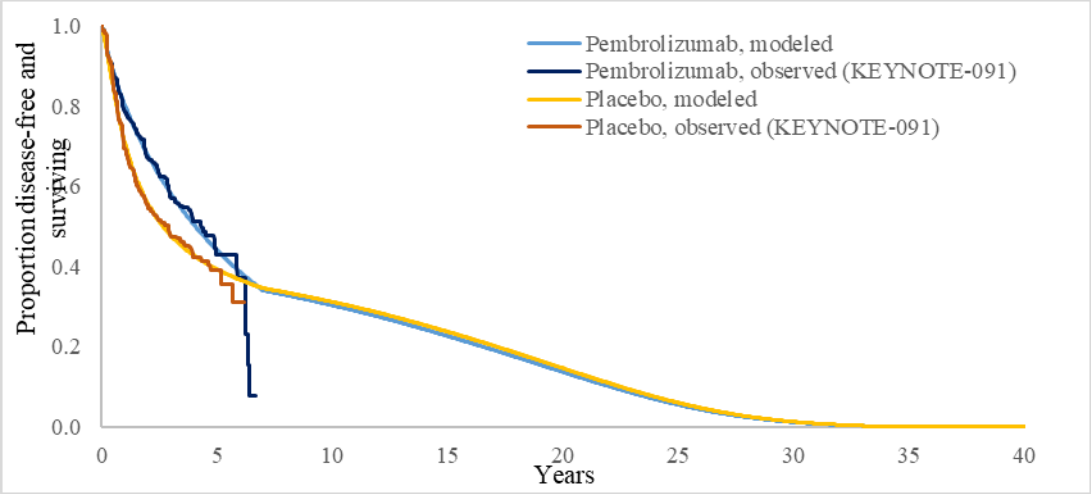


While the chi-squared value means the null hypothesis of hazards being proportional cannot be rejected, these tests are typically underpowered and may fail to reject the null even when it is false, therefore, graphs are often used to investigate if the assumption is violated.[55] The Schoenfield residual plot appears to show a pattern inconsistent with proportional hazards. A flat line would indicate a mean covariate effect over time and therefore proportional hazards.

Table 42. DFS Schoenfield residual plot

In prior submissions for this indication, atezolizumab (TA823)[34] and osimertinib (TA761),[36] the EAG and committee accepted a conservative base case, which assumed a different cure-point for the intervention compared to placebo, was plausible. In TA823 the cure point was 6 to 7 years for atezolizumab and 5 years for active monitoring and in TA761 the cure point was 5 years for active monitoring and between 5 and 8 years for osimertinib. This was to address a lack of data and significant uncertainty in the trajectory of DFS following the trial period. In addition, TA823 did not accept the company ramping up to the cure in order to avoid a sharp kink in the DFS curve. In this appraisal, the EAG has accepted the kink as the data available are more mature. In addition, if an abrupt kink was used in the EAG's updates to the preferred DFS curves it would result in placebo becoming more effective than pembrolizumab after 7 years (as shown in Figure 17), which would be an excessively conservative assumption given the information available.

Figure 17. EAG base case scenario DFS curves: cure at 7 years



The first submission to use a 95% reduction in risk was in the adjuvant treatment of HER2-positive early breast cancer (TA569).[56] The EAG, in this submission, requested the use of the 95% cure rate in conjunction with a 36-month cure point in order to obtain a 10-year recurrence rate in line with the 1.08% recurrence rate seen in Takeuchi *et al*. 2009;[57] a study on the long term recurrence rate of patients with breast carcinoma. Given this value was produced specifically for the model and HER2-positive early breast cancer, the EAG in the current appraisal requested, at clarification, an updated estimate of the cure related reduction in risk value using Sonoda *et al.* 2019,[58] which includes data for NSCLC. The company did not update the cure rate as they identified that the proportion of ultra-late recurrences (0.8%) appeared in line with the current modelled prediction of these in the control arm (0.73%).

Clinical experts have advised the EAG that even patients who remain disease free will experience a mortality rate 50-60% higher than the general population. As a result, the EAG requested, at clarification, the option to apply an SMR (standardised-mortality-ratio) to disease free patients. The company scenario using an SMR of 1.5 resulted in an ICER of [redacted]. The company noted that the all-cause mortality at year 15 in the model is already approximately 1.5 times general population and argued that there is a lack of cited empirical evidence for the SMR. The EAG has since identified an external source, West *et al.* 2023,[59] which appears to validate the company base case assumption for mortality, showing that at 9 years approximately 60% of disease-free patients remain alive. It should be noted that this was not obtained by an SLR and the clinical expert's rationale for the raised mortality was due to lasting damage to lungs from the cancer and surgery.

4.2.5.2 Local-regional recurrence

As KEYNOTE-091 did not provide robust data on further progression once a recurrence occurred, an external source was used to derive transitions from local-regional recurrence to distant metastatic recurrence and to death. The external source used was the SEER-Medicare database derived from US patients on the Medicare scheme.[40] Notably only those over 65 in the USA can qualify for Medicare.

A total of 392 patients met the inclusion criteria of patients with completely resected stage IB-IIIA NSCLC and as having a local-regional recurrence at least 30 days prior to any metastatic occurrence. The criteria were made to match the ITT population of the trial as opposed to the narrower target population of this submission; patients were not limited to those with prior adjuvant platinum-based chemotherapy who had a PD-L1 TPS <50%.

Cause specific hazards, LR to DM and LR to death, were modelled using exponential functions. This was a simplifying assumption that meant hazard rates were not dependant on time since entry. Values used for weekly transition probabilities are listed in Table 49. Like DFS the mortality rate was set to be at least as high as the general population.

Table 43. Transition probabilities (uncalibrated) starting from local-regional recurrence (SEER-Medicare)[40]

LR to DM		LR to Death	
Weekly exponential rate	**SE**	**Weekly exponential rate**	**SE**
0.00526	0.000347	0.00160	0.00019
Abbreviation: DM, distant metastases; LR or LRR, local-regional recurrence; NSCLC, non-small cell lung cancer; SE, standard error.			

The SEER-Medicare data was validated against several other external sources, with these summarised in Table 44. Notably, the transition rate used in the osimertinib company submission (TA654) was double that derived from SEER-Medicare, although patients in this study possessed a different genetic mutation as a requirement for inclusion. At clarification the EAG requested the company provide scenario analysis using these alternative sources, though the company stated there was not time available to implement this.

Table 44. SEER-Medicare versus other external sources for LR rates to DM and LR to death

Sources	Progression (LR to DM)		Overall survival (LR to Death)	
	Median progression (m)	Estimate weekly rate	Median OS (m)	Estimate weekly rate
Used in the base-case				
SEER-Medicare (without calibration)	N/A	0.00526	N/A	0.00160
Other external sources				
CancerLinQ database analysis (TA761)	15	0.011	N/R	N/R
Nakamichi 2017, CRT and RT (TA823)	11.6	0.014	34.4	0.005
Nakamichi 2017, CRT only (TA823)	19	0.008	79.6	0.002
Kruser 2014 (TA823)	N/R	N/R	5.1	0.031
PACIFIC trial, durvalumab arm (TA798)	24.9	0.006	63.1	0.003
PACIFIC trial, placebo arm (TA798)	5.5	0.029	29.6	0.005
Moore 2020, curative	N/R	N/R	34.3	0.005
Moore 2020, palliative	N/R	N/R	9.8	0.016
Abbreviations: DM, distant metastases; LR or LRR, local-regional recurrence; N/R: not reported; SE, standard error; m, months.				

As identified by the company, the SEER-Medicare data transition rates from LR to DM provides the lowest transition rates of all sources, yet it was selected due to clinicians stating the patient characteristics were the most applicable. A limited argument is made by the company for why SEER-Medicare is the most representative of the UK population. It is noted that Impower010 and SEER-Medicare were the most preferred of the available sources. The NICE Osimertinib submission source was not considered appropriate due the biological difference in patients and PACIFIC trial data is too pessimistic. Patient360 data has too many stage 1 patients leading to optimistic outcomes, but no further explanation is provided as to why SEER-Medicare is the preferred option. The key criticisms levied at the SEER-Medicare data by the company's advisory board were: (i) the population is significantly older than the KEYNOTE-091 trial; (ii) time to progression is too optimistic given the patient characteristics. Changes in local-recurrence transition rates have limited impact to the model ICER as few patients locally recur and much of the treatment benefit comes from calibrating transitions, which will be adjusted to any change in inputted values.

4.2.5.3 Distant metastatic recurrence

In each adjuvant treatment arm, the transition probability from distant metastases to death depended on the first-line treatments received. Survival within the metastatic state was assumed to be influenced by first-line therapy alone, with distribution of second-line treatments only impacting cost within the model.

The pembrolizumab arm was further divided by I/O eligibility, which would determine the market share of first line treatments. All placebo patients were I/O eligible while patients in the pembrolizumab arm would be I/O eligible if they transition to DM after having achieved at least 18 months since the start of the model. Market share of first- and second-line treatment by arm and I/O-eligibility is shown in Table 45. The first line market share in this table was used in combination with the OS data found in Table 46 to produce the exponential hazard rates by I/O eligibility and treatment arm found in Table 47. This is what was used to determine DM to death transition, with this (as with all mortality transitions) constrained to be at least equivalent to the weekly mortality rate for the general population.

Table 45. Subsequent treatment market shares by I/O eligibility status and adjuvant treatment arm (copy of table 40 from CS)

	Pembrolizumab[60]		Active monitoring
First line:	**I/O-eligible (1L)**	**I/O-ineligible (1L)**	**I/O-eligible (1L)**
Osimertinib	15%	15%	15%
Pembrolizumab + carboplatin + paclitaxel	32.6%	0%	32.6%
Pembrolizumab + pemetrexed + platinum	52.4%	0%	52.4%
Carboplatin + paclitaxel	0%	32.6%	0%
Pemetrexed + platinum (PDC)	0%	52.4%	0%
Second line:	**IO-eligible (2L)**	**IO-ineligible (2L)**	**IO-eligible (2L)**
Docetaxel	30%	30%	30%
Pemetrexed + platinum	30%	30%	30%
No active treatment (BSC)	40%	40%	40%
Abbreviations: I/O, immunotherapies; 1L, first line; 2L second line; PDC, platinum doublet chemotherapy			

Table 46. Exponential models of OS and PFS with reference treatments in the 1L metastatic NSCLC setting (copy of table 41 from CS)

Metastatic regimen	Indicated population strata	OS	PFS	Sources
		Weeks	Weeks	
Pembrolizumab + pemetrexed + platinum	Non-squamous PD-L1 < 50% NSCLC	124	51	KEYNOTE-189 data on file (data cut-off date: 08 Mar 2022)

Pembrolizumab + carboplatin + paclitaxel	Squamous PD-L1 < 50% NSCLC	103	41	KEYNOTE-407 data on file (data cut-off date: 23 Feb 2022)
Osimertinib	EGFR+ NSCLC (assumed efficacy for proportion on targeted therapy)	242	119	Ramalingam et al. (2020) [61] & Soria et al. (2018) [62]data on file [FLAURA]
Pemetrexed + platinum	Non-squamous PD-L1 < 50% NSCLC	73	32	KEYNOTE-189 data on file (data cut-off date: 08 Mar 2022)
Carboplatin + paclitaxel	Squamous PD-L1 < 50% NSCLC	73	26	KEYNOTE-407 data on file (data cut-off date: 23 Feb 2022)
Abbreviations: EGFR: epidermal growth factor receptor; NSCLC; non-small cell lung cancer; PD-L1: programmed death-ligand 1; SE: standard error				

Table 47. DM to death weighted exponential HR based on market share (copy of table 43 from CS)

Patient Group	Distant metastases → death: Weighted exponential hazard rate based on market share
Pembrolizumab (I/O eligible)	0.0074
Pembrolizumab (I/O ineligible)	0.0101
Placebo	0.0074
Abbreviations: I/O, immunotherapies	

4.2.5.3.1 Adjustment and calibration

The company validated OS, both against its own trial data, and against their preferred real world observed cohort data. As a result of this validation the company noted the results differed significantly from both the real-world OS data and the trial data. As a consequence, they opted to make adjustments so results would better match both of these sources of OS data.

The transition from DM to death was also adjusted in the company base case to match the observed SEER-Medicare data. This is because, when the age of the cohort is adjusted to match the SEER-Medicare baseline age, the mortality rate predicted for placebo patients from DM to death significantly exceeds that observed in SEER-Medicare. Applying this adjustment notably increases survival of placebo patients (decreasing the cost-effectiveness of pembrolizumab).

When compared to the KEYNOTE-091 trial data, OS in the placebo arm appeared to match that shown in the trial. However, pembrolizumab survival appeared to be severely underpredicted compared to trial OS when pembrolizumab and routine surveillance are considered equivalently effective post-recurrence. This is illustrated in Figure 18 which shows uncalibrated predicted OS for pembrolizumab in the model significantly deviates from the trial.

Figure 18. Completely uncalibrated modelled OS vs observed OS

The company's clinical advisory board speculated on two potential mechanisms of action that could cause pembrolizumab to improve efficacy post-recurrence:

1. The mechanism of immunotherapy fundamentally alters the disease trajectory, potentially impacting prognosis by either slowing overall disease progression or enabling recurrence at stages more amenable to radical treatment.
2. Immunotherapy enhances patients' sensitivity to chemotherapy in NSCLC, potentially enhancing the effectiveness of subsequent treatments like chemo-radiotherapy.

The company opted to calibrate LR to DM, LR to Death and DM to Death simultaneously in order to produce good visual fit to the OS curves. This was, in the base case, done in both arms. Including the SEER-Medicare adjustment, the calibration factor of 0.82 applied to all downstream TPs in the pembrolizumab arm and a calibration factor of 1.21 applied to downstream TPs in the placebo arm. This change produced the OS seen in

Figure 19. Calibration was not required for the placebo arm and had minimal impact but was applied in order to be consistent with the approach to both arms.

Figure 19. Real-world adjustment factor and calibration applied to both arms vs observed OS

4.2.5.3.2 EAG critique

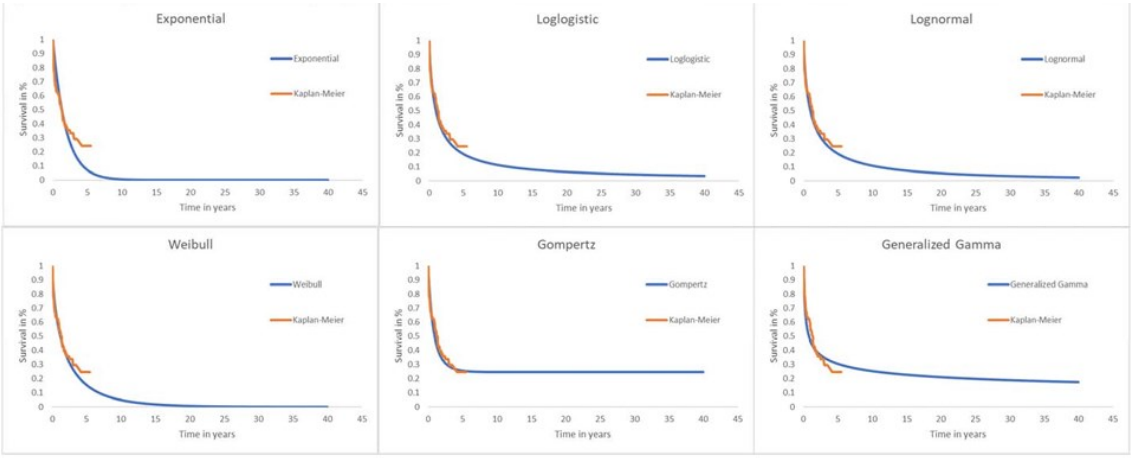
There are insufficient trial data from KEYNOTE-091 to inform transitions for patients who have recurred. The company accounts for this by using Medicaid registry data for locally-recurred patients and trial data from relevant subsequent treatments for patients with distant metastases. Due to the nature of the model, the company suggested it would be too computationally complex to include time-dependent downstream transitions, therefore transitions derived from these data are assumed to be represented by exponential curves. Using these data in the pembrolizumab arm results in a significant deviation from the trial OS results. In order to closer match the OS results from the trial a multiplier was calculated for the transitions rates for locally recurred patients to calibrate the model OS curve, so it better matches the trial results for pembrolizumab and placebo. This means the company's modelling of patient's post-recurrence relies on 3 key assumptions:

1. Exponential curves provide a reasonable fit for the external data used to derive the trajectory of patients transitioning from recurrence.
2. The relative transition rates/trajectory derived from the external data are accurate (i.e. the ratio of LR to DM compared to DM to death).

3. To match trial outcomes all values (for each treatment arm), need altering using a single universal multiplier to match trial outcomes.

There is reason to be sceptical of all 3 of these assumptions. Given the EAG does not have access to the IPD for either SEER-Medicare or the external trial sources we cannot test the goodness of fit for the exponential curves. However, in the osimertinib submission for adjuvant treatment of NSCLC, the company showed exponential to be the worst fitting of all models in representing local recurrence to distant metastatic recurrence, as demonstrated in Figure 20. This submission did use CancerLinQ data as opposed to SEER-Medicare but given it is the same condition there is no reason to think the trajectory of patients would not be similar.

Figure 20.Extrapolation of LRR to DM1 (copy of figure 26 from TA761 ACD)[36]



Abbreviations: DM1, 1st line distant metastasis; LRR, locoregional recurrence; TP4, transition probability 4.

As suggested by the EAG in section 4.2.5.1.5, there is evidence of treatment effect waning in the disease-free survival curves. This means different distributions should be used to model the two treatment arms. Given this, it seems an unlikely assumption that the same distribution and relative transition rates will apply to both treatment arms.

Finally, assuming a single multiplier, for each treatment arm, applies to all transitions equally seems unlikely. Part of this is because the data for local recurrence and distant metastatic recurrence comes from registry and trial data, respectively. Different sources are unlikely to be similar enough that using a single adjustment factor would be valid. Even if the treatment benefit for pembrolizumab did require adjusting LR to DM, LR to death and DM to death by a single consistent factor, these sources of data are highly likely to be too dissimilar to be equally generalisable to this population. They would likely require a different adjustment factor even if the same adjustment factor would be valid to use if a coherent data set were available.

The EAG does not have an alternative solution for how OS outcomes can be aligned with the trial but wants to highlight the significant uncertainty with the current modelling methods used. This is **Key issue 4** referenced in section 1.1.

In the executive summary of the advisory board, it is stated that, "A conservative approach should be taken and the treatment effect should be capped at 5 years (i.e. the end of the observed follow-up period)". However, as the cure is implemented as a linear reduction in risk progressing to 95% between years 5-7, an ongoing treatment benefit is retained by pembrolizumab after 5 years. At clarification the EAG questioned this inconsistency and requested the company provide a scenario where the treatment effect is equalised at 5 years. The company responded by noting that the clinical advisors were referring only to calibration of transition probabilities to match OS from the trial. However, even if this is what is referred to the model still uses the calibrated transition rates after 5 years, which is acknowledged by the company. They state that this is indirectly addressed by the gradual cure rate between years 5-7. As a result, the EAG base case, acting on the advisory board advice from the company, has limited calibration to 5 years as a conservative assumption. This is **Key issue 5** referenced in section 1.1.

The calibration factor applied to DM to death transitions, in order to have OS match the trial data, results in the transition rate to death for I/O ineligible patients in the pembrolizumab arm to be lower than placebo patients who will be actively treated with immunotherapies. Due to the clinical implausibility of this, at clarification the EAG requested the company provide an option to not calibrate the I/O ineligible patient arm. The company provided this, although as the calibration is forcing OS to fit the trial data including this results in a much lower OS for I/O eligible patients. Nevertheless, if the calibration is used, this should not be applied to I/O ineligible patients since the transitions otherwise appear implausible. This is **key issue 6** referenced in section 1.1.

To solve the underestimation of OS issue the EAG requested the company attempt to provide a scenario using parametric models, based on appropriate trial data, to inform the DM to Death transition rate (similar to how DFS has been modelled). The company stated this was computationally complex and impossible in the time permitted. This is a significant limiting factor to the Markov approach when compared to a partitioned survival model, since the fit for follow on-transitions is assumed to be appropriately modelled with an exponential distribution.

4.2.6 Health-related quality of life

4.2.6.1 Health state utility values

Health state utilities in the DF, LR and DM (pre-progression) health states are informed by health-related quality of life (HRQoL) data collected in the KEYNOTE-091 trial (January 2023 data-cut) using the EQ-5D-3L. For HRQoL in the DM health state, utility values to represent post-progression were taken from KEYNOTE 189/407, the pivotal trials of pembrolizumab for metastatic NSCLC (further detail provided below).

Utility values calculated from KEYNOTE-091 were based on a descriptive analysis of patient visits in which EQ-5D-3L was collected for each health state. The company's analysis treated multiple visits per participant as independent observations and therefore did not account for the correlation among repeated measures within an individual.

For the DF health state, in the company's base case analysis, the utility value excludes any patient visits in which adverse events (AEs) of any grade were reported. The company stated that due to the long-time horizon of the model and the average length of time in which patients can remain in the DF health state, it was not deemed appropriate to apply a utility value which included short -term grade 1 and 2 adverse events related to treatment. The company also provided an alternative option for the DF health state utility value which was calculated based on the weighted average of utility values for patients who were: disease free and experiencing no AEs, and patients who were disease free and experiencing grade 1-2 AEs.

Utility value for patients in the LR health state is based on the average of patients with locoregional recurrence in KEYNOTE-091, based on 463 patient visits from 179 patients.

As the company use one health state for distant metastases, in which patients receive first- and second-line treatments based on progression status, separate data sources informed HRQoL associated with DM pre-progression and DM post-progression. The company considered HRQoL data for DM from KEYNOTE-091 to be too limited to reflect the entire post-progression period in distant metastases due to the available follow up time. Therefore, utility values for DM pre-progression were based on the average utility value of patients experiencing DM in KEYNOTE-091 (0.743), while post-progression was based on pooled KEYNOTE 189 and 407 data (0.668). Due to the use of one health state for DM, the overall health state utility value used was the weighted average of the utility values for DM pre-progression and DM post-progression. The weighting applied was based on the estimated ratio of time spent in PFS to OS for the treatments included in the economic model for

metastatic disease. As treatments used in the metastatic setting differ based on previous treatments received and immunotherapy eligibility (see Section 4.2.5.3), a separate PFS:OS ratio is used for patients who are eligible for immunotherapy and those who are not, as shown below in Table 48.

Table 48. Ratio of time spent in progression free survival to overall survival based on treatments used in the metastatic setting, used to inform overall DM utility value.

Treatment arm	Eligible for re-challenge or immunotherapy in the metastatic setting	Proportion of time spent in PFS for distant metastases
Pembrolizumab	Yes	0.428
Pembrolizumab	No	0.438
Placebo	Yes	0.428

Abbreviations: OS, overall survival; PFS, progression-free survival

The utility values used in the company's base case economic model for each health state are shown below in Table 49.

Table 49. Health state utility values used in the company's base case model

Health state	Utility value	Source
Disease free	0.852	KEYNOTE-091, excluding all visits in which AEs of any grade occurred.
Locoregional recurrence	0.776	KEYNOTE-091, locoregional recurrence.
Distant metastases (eligible for immunotherapy)	0.700*	Calculated. KEYNOTE-091, distant metastases utility; pooled KEYNOTE 189 and 407; and weighting for time spent in PFS versus progressed survival.
Distant metastases (not eligible for immunotherapy)	0.701†	Calculated. KEYNOTE-091, distant metastases utility; pooled KEYNOTE 189 and 407; and weighting for time spent in PFS versus progressed survival.

* (KEYNOTE-091 DM utility [0.743] x proportion of time spent PF [0.428]) + (KEYNOTE-189/407 [0.668] x proportion of time spent progressed [0.572])

† (KEYNOTE-091 DM utility [0.743] x proportion of time spent PF [0.438]) + (KEYNOTE-189/407 [0.668] x proportion of time spent progressed [0.562])

Abbreviations: OS, overall survival; PFS, progression-free survival.

4.2.6.2 Age-adjustment

The company's model used Ara and Brazier 2010 to apply age-related utility decrement.[63] As a result of a clarification request, the company updated the model to use the Health Survey for England

(HSE) 2014 dataset, as recommended by the NICE decision support unit (DSU) (Hernández Alava *et al.* 2022).[64] The company applied age adjustment to utility values starting from the mean age of the trial (64.3 years) plus the average trial follow up period (3.9 years). The company state that this approach is used as the utility values from the KEYNOTE-091 trial already reflect the mean age of participants during the trial period.

4.2.6.3 Adverse event disutility

The company applied a one-off utility decrement in the first model cycle for grade 3+ adverse events (AEs) in both the pembrolizumab and placebo arms. The utility decrement applied in the model is a function of the AE disutility value, the proportion of patients experiencing adverse events, average number of events and average duration of each AE experienced.

The disutility value applied was obtained from the KEYNOTE-091 trial and was calculated as the difference between the average EQ-5D value of patients who were disease free with no AEs and those who were disease free and experiencing grade 3+ AEs, at the time of patient visits. The company used data from all patients, regardless of treatment arm, in the calculation of AE disutility. Therefore, the disutility value applied for AEs was the same for both the pembrolizumab and placebo arms of the model, equal to -0.116.

The proportion of patients experiencing adverse events, average number of episodes and average duration of each AE experienced was informed by KEYNOTE-091. The proportion of patients experiencing each type of grade 3+ AE is treatment arm specific, whereas the company pooled data from both arms of the KEYNOTE-091 trial for the average number of episodes and the average duration of AE. During the clarification process, the EAG requested that the company provided this data for each treatment arm rather than pooled. Although this data was provided, due to the model structure this was unable to be incorporated into the economic model by the company.

In the company base case, the overall one-off utility decrement for AEs applied in the model was -0.01554 for pembrolizumab and -0.01581 for placebo. This suggests a greater disutility for placebo than pembrolizumab, albeit extremely small.

4.2.6.4 EAG critique

The EAG agrees with the company's use of EQ-5D-3L data collected from the key trial to inform health state utility values. However, the EAG consider there to be a number of limitations on the data analysis performed, discussed further below.

As previously noted, health state utility values calculated from KEYNOTE-091 were based on the average of EQ-5D-3L for all patient visits. Therefore, this did not account for the correlation among repeated measures for an individual. During clarification, the EAG requested that the company provided EQ-5D utility values for each health state (including disease-free with grade 1-2 AEs) using appropriate mixed-effect regression models. The company provided utility values obtained using a linear mixed-effects regression model with patient level random effects. The analysis for DF utility values controlled for adverse events to provide estimates of utility without grade 3+ AEs and without grade ½ AEs. The EAG notes that no further covariates were considered for inclusion in the regression model, such as baseline utility or prognostic factors.

Utility values derived from the regression analysis are provided in the table below, alongside those measured using the descriptive analysis.

Table 50. Utility values derived from regression approach versus descriptive analysis

Health state	Utilities measured via regression approach	Utilities measures via descriptive analysis (company base-case)
Disease-free (without grade 3+ AEs)	0.801 (0.005)	0.806 (0.007)*
Disease-free (without grade 1/2 AEs)	0.811 (0.006)	0.852 (0.012)
Local-regional recurrence	0.765 (0.012)	0.776 (0.026)
Distant metastases (pre-progression)	0.712 (0.011)	0.743 (0.022)

*Not used in company base-case

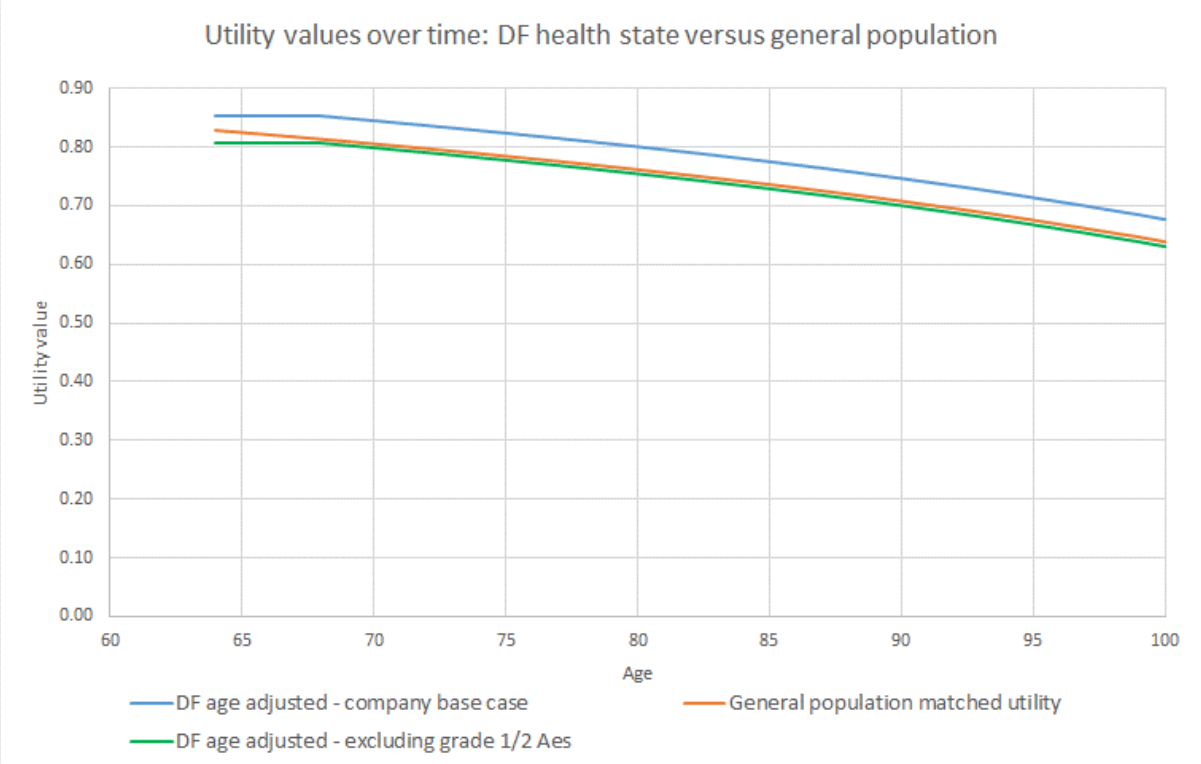
Abbreviations: AE, adverse events

The company argued that while a regression approach accounting for repeated measures was considered and conducted in response to clarification, it was deemed inappropriate for use in the base-case analysis. The company consider a descriptive analysis more appropriate in the context of oncology trials due to correlations being present between patients with repeated measurements and the overall outcome (utility value). For example, patients with single measures are more likely to have either died, had disease progression or be in worse health, i.e. data are not missing at random. While the EAG agrees that assuming data are not missing at random may be plausible, a descriptive analysis may be equally biased. As such, the company did not run a scenario using the utility values derived from the regression analysis and instead the EAG has provided a scenario analysis with these values used (see Section 6).

For their base case analysis, the company excluded grade 1 and 2 AEs from the descriptive analysis of EQ-5D values for the disease-free health state, with an alternative value provided in which the AEs

were included. The resulting utility value used in the company's base case analysis for DF (0.852) is higher than the age and sex matched general population norm, despite age adjustment being included over time. The EAG do not consider this to be plausible. This is shown in Figure 21, which also includes an alternative value for the DF health state, which includes grade 1/2 AEs. The EAG's clinical experts also noted that they would not consider it likely that DF patients would have the same HRQoL as age and sex matched general population as patients who have undergone invasive treatments can experience lifelong consequences. The use of this implausible utility value for DF favours the pembrolizumab arm of the model. The EAG consider the value for DF including grade 1/2 AEs (0.806) to be more appropriate and thus includes this in the EAG base-case analysis. This is **Key issue 7** referenced in section 1.1.

Figure 21. Utility values over time for the disease free health state versus general population



Abbreviations: AEs, adverse events; DF, disease free

As discussed previously, the average number of AE episodes and average duration of AEs informing the one-off utility decrement was based on pooled data from both arms of the KEYNOTE-091. The EAG considers it to be inappropriate to use pooled rather than treatment specific data as the duration and number of episodes differs for those patients receiving active treatments (i.e. pembrolizumab). The EAG therefore deems it more appropriate to calculate the one-off utility decrement based on treatment specific AE frequencies and duration. However, during clarification

the company noted that due to restrictions in the model structure, this was unable to be incorporated in the time frame. The company instead ran scenario analyses using either just AE data specifically for pembrolizumab or placebo and found the impact on the ICER was minimal. This is also discussed in relation to costs in Section 4.2.7.7.

4.2.7 Resource use and costs

The company's model includes costs related to drug acquisition for adjuvant and subsequent treatments, drug administration, disease management costs, adverse events (AEs), PDL1 testing and end-of-life care. These are detailed further in the following subsections. Costs used in the model represent 2021/22 prices.

4.2.7.1 Treatment costs

A patient access scheme (PAS) discount is in place for adjuvant pembrolizumab, detailed below. Confidential PAS discounts/CMU prices are also available for a number of subsequent treatments included in the economic model. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses. Please refer to Appendix 8.1 for details on the source of the confidential price for each treatment.

Drug acquisition costs – adjuvant treatments

Adjuvant pembrolizumab has a list price of £2,630 per 100mg intravenous (IV) vial and is administered at a dose of either 200mg every three weeks (QW3) or 400mg every six week (QW6), as stated in the SmPC. In the company's base case model, a dose of 200mg every three weeks is used. A simple PAS discount is available for adjuvant pembrolizumab, resulting in a price of [redacted] per 100mg vial. All results presented in this report include the corresponding PAS price.

The number of doses received in the economic model was based on the maximum dosage received in the KEYNOTE-091 trial, which is in line with the SmPC guidance of treatment until disease recurrence, unacceptable toxicity or for a duration of up to one year. As pembrolizumab is given at a rate of once every three weeks in the economic model, this corresponds to a maximum of 18 doses within one year, when starting at cycle zero. To estimate pembrolizumab acquisition costs, the proportion of patients receiving treatment at each cycle is based on fully mature time on treatment (ToT) Kaplan-Meier (KM) data from KEYNOTE-091, shown in Figure 22. Due to a small proportion of

patients having early delays in treatment, the KM data shows patients receiving treatment beyond one year (dashed line in Figure 22), yet no patients received more than 18 treatment cycles. In the company's base case model, the company assumed 100% relative dose intensity (RDI) and truncated the KM curve at 52 weeks. The company also provided a scenario analysis in which the full KM curve was used and the corresponding RDI from KEYNOTE-091 of [redacted] was applied. The approach used had a minor impact on the resulting ICER.

Figure 22. Time of treatment Kaplan-Meier data from KEYNOTE-091, used to inform drug acquisition costs. Reproduced from Figure 18 of CS

No drug acquisition costs were applied in the standard of care arm for adjuvant treatment due to disease management consisting of routine surveillance only, prior to disease progression (see following section for subsequent treatment costs).

Treatment costs – locoregional recurrence

Active subsequent treatments upon locoregional recurrence are assumed to consist of chemotherapy, with a proportion also receiving radiotherapy (chemoradiation). Based on the company's clinical expert advisory board, 60% of patients with locoregional recurrence are assumed to receive chemotherapy (30% chemotherapy alone and 30% chemoradiation). The remaining 40% of patients are assumed to receive either radiotherapy alone (20%), best supportive care (18%) or salvage therapy (2%), discussed in further detail below. All costs related to locoregional recurrence are applied as a one-off cost at the point of entry to the model health state.

Clinical experts to the company suggested that vinorelbine + cisplatin would be the most commonly used chemotherapy treatment for patients with locoregional recurrence. Based on prescribing data, the dosing schedule is vinorelbine 25mg/m^2 IV once weekly and cisplatin 100 mg/m^2 IV once every four weeks. Unit costs for both drugs are sourced from eMIT prices.[65]

Time on treatment (ToT) with vinorelbine + cisplatin is assumed to be 6.9 weeks. This is based on the average duration for patients treated with vinorelbine + cisplatin for locoregional recurrence from the KEYNOTE-091 trial. The dosage used in the model based on mean body surface area (BSA) of patients in KEYNOTE-091 is shown in Table 51 alongside estimated acquisition costs.

Table 51. Dosage and drug acquisition costs for locoregional recurrence

Treatment	Dose per administration (mg/m^2)	Mean body surface area (m^2)	Required dose (mg)	Strength per unit (mg)	Cost per unit	Units required per administration	Drug acquisition cost per administration
Vinorelbine	25	1.9	48	50	£15.86	1	£15.86
Cisplatin	100		190	50	£5.58	4	£22.32
Abbreviations :mg, milligrams							

The cost of radiotherapy (applied to 50% of LR patients; 20% radiotherapy only, 30% chemoradiotherapy) was originally based on a combination of CHART, hyper fractionated and standard fractionated radiotherapy. The EAG was unable to verify the total cost used for radiotherapy based on the information provided. Clinical advisors to the EAG stated that no patients would receive hyper fractionated radiotherapy and that the split between patients receiving standard fractionated and CHART would be 95% and 5%, respectively. Additionally, on average 20 fractions of treatment would be delivered during standard fractionated radiotherapy. During clarification, as the company was unable to provide evidence to support their original costs, this was updated in line with the EAG's suggestion. The costs used for radiotherapy in the model are shown below Table 52 along with the unit cost for salvage therapy.

Table 52. Unit costs and calculations for salvage therapy and radiotherapy applied in the LR health state

Resource	Resource use	Cost	Source
Salvage surgery	1	£11,273	NHS National Schedule of Reference Cost 2021/22: DZ02H-K, Complex Thoracic Procedures, 19 years and over, with CC Score 6+ CC Score 0 to 6+, elective inpatients (weighted average)
Continuous Hyperfractionated Accelerated Radiotherapy (CHART)			

Define volume for simple radiation therapy with imaging and dosimetry	1	£790	Unit cost from NHS National Schedule of Reference Cost 2021/22 -SC45Z. Resource use from CG121.
Deliver a fraction of complex treatment on a megavoltage machine	1	£212	Unit cost from NHS National Schedule of Reference Cost 2021/22 – SC23Z. Resource use from CG121.
Deliver a fraction of treatment on a megavoltage machine	35	£178	Unit cost from NHS National Schedule of Reference Cost 2021/22 – SC22Z. Resource use from CG121.
Number of days of hospital inpatient stay	12	£4,239	NG122 cost inflated from 2017 to 2022 using CPI (2017 costs first 5 days - £1,590 + 7 Excess bed days (£313 each). Cost shown is total cost of 12 inpatient days.
Total cost of CHART	£11,457		Calculation
Standard fractionated radiotherapy			
Define volume for simple radiation therapy with imaging and dosimetry	1	£790	Unit cost from NHS National Schedule of Reference Cost 2021/22 -SC45Z. Resource use from CG121
Deliver a fraction of complex treatment on a megavoltage machine	1	£212	Unit cost from NHS National Schedule of Reference Cost 2021/22 – SC23Z. Resource use from CG121
Deliver a fraction of treatment on a megavoltage machine	19	£178	Unit cost from NHS National Schedule of Reference Cost 2021/22 -SC22Z. Resource use from CG121
Total cost of standard fractionated radiotherapy	£4,376		Calculation
Total radiotherapy costs			
Total cost of radiotherapy used alone	£4,376		Cost of standard fractionated radiotherapy
Total cost of radiotherapy used as part of chemoradiotherapy	£4,730		Weighted average. 5% CHART, 95% standard fractionated radiotherapy. Updated by the company during clarification to reflect the EAG clinical experts advice.
Total radiotherapy cost for use in the model	**£4,518***		Weighted average. 30% receiving cost of radiotherapy alone, 20% receiving cost of radiotherapy when used as part of chemoradiotherapy

*This cost is applied to 50% of patients as a one-off entry cost to the LR health state to represent the 50% of patients receiving any form of radiotherapy

Abbreviations: CG, clinical guideline; CHART, Continuous Hyperfractionated Accelerated Radiotherapy; CPI, consumer price index; EAG, external assessment group; NG122; NICE guideline; NHS, National Health Service

Treatment costs – distant metastases

Patients with distant metastases receive first- and second-line treatments in the economic model. First-line treatment is determined by a patient's immunotherapy eligibility, whereas second-line treatment is the same for all patients, irrespective of previous treatments or treatment arm. Costs for distant metastases treatments are applied as a one-off cost upon model entry to the DM health state. Relative dose intensity (RDI) is assumed to be 100% for all distant metastases treatments, including pembrolizumab.

First-line treatments for distant metastases consist of the treatments and dosage shown in Table 53. The proportion of patients receiving each treatment is based on immunotherapy eligibility and treatment arm, as previously discussed in Section 4.2.5.1.3.

In Table 59 of the CS it was noted that for patients receiving carboplatin + (nab-) paclitaxel regimens, with or without pembrolizumab, a proportion of patients will receive nab-paclitaxel and the remainder will receive paclitaxel. However, in the economic model, 100% of patients receive paclitaxel as part of the regimen. During clarification, the company stated that no patients are assumed to receive nab-paclitaxel in UK clinical practice and 100% would receive paclitaxel.

Both carboplatin and cisplatin are used as part of platinum-based chemotherapy, with the proportion of patients receiving each informed by the KEYNOTE-189 trial. When used in combination with pembrolizumab + pemetrexed for those patients eligible to receive immunotherapy for distant metastases, 72.4% are assumed to receive carboplatin and 27.4% receive cisplatin. When used in combination with pemetrexed only, 71.8% receive carboplatin and the remaining 28.2% receive cisplatin.

Table 53. Dosage and drug acquisition costs for first-line distant metastases

Regimen	Treatment	Dose per administration	Strength per unit (mg)	Cost per unit (tablet/vial)	Units per administration/ pharmacy dispensing*	Drug acquisition cost per administration
Osimertinib	Osimertinib	80 mg (daily)	80	£192.33	28	5,385.33
Carboplatin + paclitaxel	Carboplatin	AUC 6 mg/ml/min IV Q3W	450	£14.69	2	£29.38
	Paclitaxel	200 mg/m^2 IV Q3W	300	£17.40	2	£34.80
	Pembrolizumab	200 mg IV Q3W	100	£2,630.00	2	£5,260.00

Pembrolizumab + carboplatin + paclitaxel	Carboplatin	AUC 6 mg/ml/min IV Q3W	450	£14.69	2	£29.38
	Paclitaxel	200 mg/m^2 IV Q3W	300	£17.40	2	£34.80
Pembrolizumab + pemetrexed + platinum therapy	Pembrolizumab	200 mg IV Q3W	100	£2,630.00	2	£5,260.00
	Pemetrexed	500 mg/m^2 IV Q3W	100	£71.43	10	£714.30
	Carboplatin	AUC 5 mg/ml/min IV Q3W	450	£14.69	2	£29.38
	Cisplatin	75 mg/m^2 IV Q3W	50	£5.58	3	£16.74
Pemetrexed + platinum therapy	Pemetrexed	500 mg/m^2 IV Q3W	100	£71.43	10	£714.30
	Carboplatin	AUC 5 mg/ml/min IV Q3W	450	£14.69	2	£29.38
	Cisplatin	75 mg/m^2 IV Q3W	50	£5.58	3	£16.74

* Units required per administration or pharmacy dispensing accounts for the target dose required for the average patient in the model based on average body surface area (1.9) and glomerular filtration rate (75)

Abbreviations: AUC, area under the concentration; mg, milligrams; m^2, square meter; ml, millilitres; IV, intravenous; Q3W, three times weekly

ToT for first-line treatments for DM was assumed to continue until progression based on exponential progression free survival (PFS) estimated for each treatment regimen. Where available, PFS curves were estimated based on exponential curves fit to median PFS from the pivotal clinical trials. When median PFS for the treatment regimen was not available, hazard ratios for PFS versus the relevant reference treatment were obtained from network meta-analyses (NMA) or head-to-head clinical trial. For regimens with a pre-specified maximum treatment duration, the ToT curve was truncated to zero at the corresponding time point (see Table 59 of CS).

During clarification, the EAG highlighted that the proportion of patients receiving treatments for second line metastases did not account for patients who would die in distant metastases and therefore not receive any second-line therapies. As the company was unable to source data on the proportion of patients whose first event in DM was death as opposed to progression, they instead increased the proportion originally assumed to receive no active treatment by 10%. This was based on a previous technology appraisal for pembrolizumab for metastatic cervical cancer (TA939)[66] in which implied 10% of PFS events that were deaths were close to 10% in both treatment arms.

Therefore, the second-line treatments for DM in the company's updated model is assumed to consist of either docetaxel (27%), pemetrexed + platinum therapy (27%) or no active treatment (46%).

Patients receiving no active treatment have no associated costs. Dosage and estimated drug acquisition costs per administration for second-line DM treatments are shown in Table 54.

Table 54. Dosage and drug acquisition costs for second-line distant metastases

Regimen	Treatment	Dose per administration	Strength per unit (mg)	Cost per unit	Units required per administration*	Drug acquisition cost per administration
Docetaxel	Docetaxel	75 mg/m2 IV Q3W	160	£16.04	1	£16.04
Pemetrexed + platinum therapy	Pemetrexed	500 mg/m2 IV Q3W	100	£71.43	10	£714.30
	Carboplatin	AUC 5 mg/ml/min IV Q3W	450	£14.69	2	£29.38
	Cisplatin	75 mg/m2 IV Q3W	50	£5.58	3	£16.74

* Units required per administration or pharmacy dispensing accounts for the target dose required for the average patient in the model based on average body surface area (1.9) and glomerular filtration rate (75)

Abbreviations: AUC, area under the concentration; mg, milligrams; m^2, square meter; ml, millilitres; IV, intravenous; Q3W, three times weekly

ToT for second-line DM treatments was based on analysis of the Flatiron database and the observed mean treatment duration for the selected treatments for adult patients previously treated with first-line treatment for advanced/metastatic NSCLC. The mean total cost of each regimen used at second-line is estimated based on the reported mean ToT.

Based on the market shares for each treatment regimen, a weighted average of drug acquisition costs for both first- and second-line distant metastases treatments was calculated. These are then added to give a total cost of all drug acquisition costs for DM. This same approach is also applied to administration costs for DM treatments. The resulting total treatment acquisition costs (undiscounted) for DM treatments was £59,521 for patients eligible for pembrolizumab for distant metastases and £29,665 for patients who are ineligible (i.e. patients who progress to DM within 18 months of starting adjuvant pembrolizumab).

4.2.7.2 Administration costs

The company applied an administration cost for IV pembrolizumab based on the simple parenteral chemotherapy at first attendance cost code (SB12Z) from NHS Reference Costs 2021/22,[67] which is equal to £287. This was applied at the beginning of each three-week treatment cycle based on the dosing used in the company's base case. This cost was only applied to the proportion of patients remaining on treatment, informed by the ToT KM curve previously discussed in Section 4.2.7.1.

While not described in the CS, separate administration costs were also applied for subsequent treatments for loco-regional and distant metastases, based on treatment regimen dosing schedules. For oral treatments (osimertinib only), activity code SB11Z (Deliver Exclusively Oral Chemotherapy) from NHS Reference Costs was applied, with an associated cost of £216.90. For all remaining subsequent therapies used in the model, administered via IV, the company used activity code SB13Z (deliver more complex parenteral chemotherapy at first attendance) with a cost of £353.64 or SB12Z (simple parenteral chemotherapy at first attendance) for docetaxel.

4.2.7.3 Disease management costs

Disease management associated with each health state was informed by health care resource use (HCRU) reported in TA823 (atezolizumab),[34] with the exception of hospitalisations, which were not reported, and instead informed by TA761 (osimertinib).[36] HCRU was validated by clinical experts during the company's clinical advisory board meeting. During the clinical advisory board, clinicians stated that they would expect hospitalisation in the DF health state to occur once every two years and therefore the company updated the resource use applied in the model. All resource use rates were converted to weekly rates, in line with the model cycle length.

HCRU was combined with unit costs associated with each resource, sourced from either NHS Reference Costs 2021/22[67] or PSSRU 2022,[68] (see Table 55) to give a per cycle cost for each health state.

Table 55. Unit costs of health care resource use for disease management, reproduced from Table 57 of CS

Resource use	Unit cost	Source
Hospitalisation	£2,879	DFS hospitalisation osimertinib (TA761) and MSD Clinical Advisory Board 2023. NHS reference costs 2021-22, DZ17L-V – Respiratory Neoplasms, with CC Score 0-10+;

		Non-elective long and short stay (weighted average).
Outpatient visit	£205.78	Per visit. NHS Reference Costs 2021-22: Code 370 outpatient medical oncology. Total HRG activity.
Community nurse	£96	Band 8b, Cost per hour nurse. Personal Social Service Research Unit in UK, 2023.
Clinical nurse specialist	£96	Assumed same as community nurse cost.
GP surgery consultation	£41	PSSRU unit costs 2022. With qualification cost, average consultation (9.22 minutes).
GP home visit	£123	PSSRU unit costs 2022. With qualification cost. Assume 3 times GP surgery unit cost.
Therapist visit	£50	PSSRU 2022 cost per hour for community occupational therapist (including qualifications).
CT chest scan	£142	NHS Reference Costs 2021-22, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast).
Chest radiography	£38.28	Per visit. NHS Reference Costs 2021-22: Direct Access Plain Film.
Electrocardiogram	£181.14	NHS Reference Costs 2021-22, Electrocardiogram Monitoring or Stress Testing, EY51Z. Outpatient procedure.
PET-CT scan	£722.11	NHS Reference Costs 2021/2022: RN01A/RN02A/RN03A – Positron Emission Tomography with Computed Tomography (PET-CT) of one/two or three/more than three areas, 19 years and over (weighted average).
MRI	£322.35	NHS Reference Costs 2021/2022: RD05Z – Magnetic Resonance Imaging Scan of more than three areas, with contrast (Imaging: Outpatient).

Abbreviations: CT, computed tomography; GP, general practitioner; MRI, magnetic resonance Imaging; PET, positron emission tomography.

In the DF health state, separate costs are applied up to the first 5 years, after which the health state costs are assumed to reduce between years 5–7, in line with the company's assumption regarding cure starting at 5 years. For patients remaining in the DF health state beyond 7 years since model entry, a minimal per cycle costs is applied (see Table 56 of CS for further details). During clarification, the company updated the number of CT scans applied in the DF health state following advice from both the EAG's and company's clinical experts. The company stated on multiple occasions that this was updated to include two CT scans a year for the first 5 years and yearly between years 5-7. However, the EAG notes that this was incorrectly applied in the model and applied two CT scans per year at all time points. The EAG has corrected this error in their updated base case to include yearly scans after 5 years only. This had a negligible impact on the ICER.

The EAG notes that during clarification, the company stated that they had corrected an error highlighted by the EAG in which CT scans for patients in LR should have been applied only to patients

on active therapy (82%). However, this correction was made incorrectly, and the company instead applied the equivalent of one CT scan per year only to 82% of patients. This should have been corrected to 4 CT scans per year applied to 82% of patients. The EAG has corrected this in its updated base-case (see Section 6).

A one-off health state entry cost is also applied to the DM health state to reflect routine appointment and scans upon progression to DM. The overall health state cost for DM is a weighted average of the costs for DM pre-progression and DM post-progression. The weighting applied uses the same data as that used for utility value in the DM health state, previously described in Section 4.2.6.1.

The per-cycle and one-off disease management costs applied in the company's updated model are provided in Table 56.

Table 56. Disease management costs as applied in company's updated base case.

Health state	Application in model	Cost
Disease free	Per 1-week cycle, years 0–5	£41.11
	Per 1-week cycle, years 5–7	£24.73
	Per 1-week cycle, years 7+	£2.36
Locoregional recurrence	Per 1 week cycle	£130.91
Distant metastases	Once off on entry of health state	£1,298.50
	Per 1 week cycle (immunotherapy eligible)	£287.67
	Per 1 week cycle (immunotherapy ineligible)	£287.08

4.2.7.4 Adverse event costs

The company applied a one-off cost in the first model cycle of each treatment arm for the management of grade 3+ adverse events (AEs) occurring in >1% in either the pembrolizumab and placebo arm. The total AE cost applied in the model is a function of the cost associated with managing AEs, the proportion of patients experiencing AEs, average number of events and average duration of each AE experienced.

The company applied separate costs for the management of AEs for those requiring hospitalisation and those not. The proportion of patients requiring hospitalisation was sourced from KEYNOTE-091 and pooled by the company for patients on placebo and pembrolizumab. The cost of each adverse

event requiring hospitalisation were sourced from NHS Reference Costs (2021/22).[67] The EAG was unable to verify a number of the costs used by the company and identified a number of inconsistencies in the specific NHS Reference Cost codes applied. Following a clarification question the company updated the costs used and chose to use the weighted average for all HRG codes associated with each event. The costs used in the company's updated base case following CQs is shown in Table 57.

Table 57. Costs of hospitalisation associated with each adverse event included on the economic model

Adverse event	Hospitalisation cost	Source
Diarrhoea	£1,422.46	NHS Reference Cost 2021/22, FD10J-M: Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-11+ – Total HRGs (weighted average)
Dyspnoea	£760.96	NHS Reference Cost 2021/22, DZ19L-N: Other Respiratory Disorders without Interventions, with CC Score 0-11+ – Total HRGs (weighted average)
Hypertension	£770.10	NHS Reference Cost 2021/22, EB04Z: Hypertension – Total HRG
Hyponatraemia	£771.47	NHS Reference Cost 2021/22, WH13A-C: Abnormal Findings without Diagnosis – Total HRGs (weighted average)
Pneumonia	£2,258.95	NHS Reference Costs 2021/2022 [DZ11R:V Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-14+ (weighted average)
Pneumonitis	£2,258.95	Assume same cost as Pneumonia
Weight increase	£0	Common Terminology Criteria for Adverse Events (CTCAE) guidelines. Assume zero cost.

For the proportion of AEs that are not assumed to require hospitalisation, the company originally applied a cost of £160.43 (NHS Reference Costs – Clinical Oncology total outpatient attendance), regardless of adverse event type. During the clarification stage, the EAG requested that the company provided a scenario analysis which used the outpatient cost associated with each specific adverse event type. While this was not provided, the company instead included a scenario which used a weighted average cost of non-admitted (face-to face and non-face-to-face) and multi-professional non-admitted (face-to face and non-face-to-face) in the outpatient setting (£163.79), applied to all AE types (see Table 29 of the clarification response). This had a negligible impact on the ICER.

Table 58 presents the total AE management cost for each treatment arm of the model.

Table 58. Total adverse event costs applied in the company base case

Treatment arm	Total AE management cost (£)
Pembrolizumab	£131.01
Routine monitoring	£79.13
Abbreviations: AE, Adverse event	

4.2.7.5 PD-L1 testing costs

The company applied a one-off cost for all patients in the adjuvant pembrolizumab arm to represent testing for PD-L1 status. The cost of the test was sourced from the previous TA for atezolizumab for adjuvant treatment of NSCLC (TA823).[34] The company estimated the proportion of PD-L1 tests required per patient entering the target population by dividing the unit cost of each test by the prevalence of PD-L1<50% in the KEYNOTE-091 trial (72%). This gave a one-off cost of £56.25.

4.2.7.6 End of life care costs

The company included a one off end-of-life cost, applied upon transition to the death health state. This cost reflects the management costs associated with terminal care. A cost of £6,207.60 was sourced from Georghiou and Bardsley 2014[69] and inflated to a 2022 value of £7,428.87.

4.2.7.7 EAG critique

While the EAG agrees with the majority of costs used in the model, there appears to be a number of issues, which are described further below. In addition, the estimation of costs used in the model was vague and obtusely described in the CS, resulting in the EAG spending an inordinate amount of time disentangling the underlying calculations used for the hardcoded values in the model. The EAG notes that the company also applied an assumed discount for osimertinib of 60% and included this in all base-case analyses, despite stating that they are unaware of the discount applied in practice. The EAG had to request that this was removed from the company's analyses more than once as the company only provided these results as a scenario in response to CQs. It is unclear to the EAG why the company's base case analyses would be provided using an assumed discount for a comparator, despite NICE guidance stating that list prices should be used when discounts are unknown.

Treatment costs

The EAG considers the use of the full KM curve from KEYNOTE-091 and the corresponding RDI of [redacted] to be more appropriate for the costing of adjuvant pembrolizumab as this corresponds to the

trial data informing the effectiveness data used in the model. This is used in the EAG's updated base case. This is **additional issue 5** referenced in section 1.5. As noted in the company's scenario analysis, this had a small impact on the ICER.

The company noted that dosing schedule of every 6 weeks may be used in clinical practice for adjuvant pembrolizumab and is included in the European Medicines Agency (EMA) marketing authorisation.[20] However, this was not used in the company base case. Clinical experts to the EAG stated that although it may vary from centre to centre, the majority of patients will receive treatment every six weeks as opposed to every three weeks as this is more convenient for patients and frees up limited resources in chemotherapy units. The EAG applied a dosing schedule of 400mg every 6 weeks for 75% of pembrolizumab patients in their base case analysis, based on the NHSE advice that initial dosing would be Q3W for the first 2-3 months, then patients would transition to Q6W. As this results in fewer administrations, this reduced the ICER. The EAG also considers the same dosing schedule to be most appropriate for pembrolizumab in the metastatic setting.

Treatment for loco-regional recurrence was assumed to consist of vinorelbine + cisplatin (30%), radiotherapy (50%), salvage surgery (2%) and no active treatment (18%). While clinical experts to the EAG largely agreed with the use of vinorelbine + cisplatin, it was also noted that durvalumab may be used for a proportion of patients. The company noted in their submission that, although durvalumab may be used for a proportion of patients after chemo-radiation, this was excluded from the economic model. They stated that this was due to the generalisability of the key trial for durvalumab being uncertain in a resected and recurred population, as used in the model, and would only relate to a specific subgroup of patients (unresectable stage III PDL1>1%). Due to the above reasons the company stated it would be extremely difficult to implement an intermediate health state in the model to represent this. While the EAG considers that the model should have been structured to accurately reflect the treatment pathway used in UK clinical practice, it considers the reasons relating to the generalisability of the evidence to be appropriate for exclusion. However, the extent to which this exclusion will affect the ICER is unknown.

The mean ToT used to estimate the drug acquisition costs for vinorelbine + cisplatin was based on the observed mean ToT in KEYNOTE-091 for patients receiving this regimen for LR. This was based on only [redacted]; the EAG considers that this may introduce uncertainty in the average costs applied for vinorelbine + cisplatin. In addition, the dosing schedule used by the company appears to be based on FDA prescribing data, in which it states vinorelbine (Navelbine®) is given at a dose of 25mg/m^2 on a weekly basis over a 28 day cycle in combination with cisplatin 100mg/m^2 on day one

of each 28 day cycle.[70] The EAG notes that FDA prescribing data may differ to UK clinical practice. Evidence found by the EAG suggests that vinorelbine + cisplatin tends to be given in the UK for a period of four cycles (21 days each), in which vinorelbine (15mg/m² [max 30mg]) is given twice in a three week cycle (days 1 and 8) and cisplatin (80mg/m^2) is given once (day 1).[71] The EAG notes that they were unable to amend this in the company's model to explore as a scenario. While the EAG notes that this is an uncertainty and limitations of the model, due to the low costs of treatments used in, the EAG does not consider this to have a significant impact on the ICER.

For first-line metastatic treatment, the company state how 15% of patients are assumed to receive a targeted therapy for EGFR, KRAS G12C, ALK, ROS-1 positive NSCLC. As each mutation has specific targeted therapies approved, for ease of modelling, the company assumed all would be given osimertinib (EGFR treatment). As discussed in Section 2.2.1, the EAG notes that if osimertinib is approved for routine commissioning following a CDF review, then no EGFR+ patients would be in this current treatment pathway and therefore would not receive adjuvant pembrolizumab followed by osimertinib in the metastatic stage. During clarification, the EAG requested that the company conducted a scenario which included data and costings for each mutation type and the corresponding targeted treatment. The company was unable to provide this in the provided time frame. The company acknowledged that the approach used introduced bias but stated that this is applied to a small proportion of patients on first-line DM treatment and is equal in both arms of the model. The company also conducted a scenario analysis in which the price of osimertinib was set to zero to show an extreme scenario and stated that this had a small impact on the ICER (≈£1,000). While the EAG note that it is a limitation of the company's model to assume all targeted therapies have the same costs and outcomes as osimertinib, the EAG is satisfied that this is not a significant driver of the ICER.

The EAG's clinical experts stated that given the average age of patients and the toxicity of cisplatin, carboplatin is preferred in clinical practice. This was also noted by the company's clinical advisors in the provided advisory board document in which it is stated that, "*A preference for carboplatin-based over cisplatin-based chemotherapy was indicated by all advisors*". Cisplatin is assumed to be part of the pembrolizumab and pemetrexed combination subsequent treatments used in distant metastases. Despite this being a simple change in the model, the company stated that this could not be implemented in time during clarification. When implementing this scenario, the EAG noted it had a negligible impact on the ICER.

Clinical experts to the EAG stated that for the treatment of second-line distant metastases, the majority of patients would be treated with docetaxel rather than pemetrexed + platinum. During clarification the EAG requested a scenario which assumed that 60% of patients are treated with docetaxel and 40% receive no active treatment. This resulted in a slight increase in the updated company base case. Based on clinical expert opinion, the EAG implemented this scenario in their base case (see section 6). This is **additional issue 6** referenced in section 1.5

As discussed in Section 4.2.7.1, drug acquisition costs for distant metastases are based on market share assumptions and PFS extrapolation based on exponential curves for all treatments. The EAG considers this to result in high uncertainty regarding the DM drug acquisition costs. The extent of the impact on the ICER due to this uncertainty is unknown.

Administration costs

During the clarification process, the EAG requested that the company used the corresponding NHS Reference Cost for subsequent administrations (i.e. after the first administration) as opposed to the cost associated with first attendance for all subsequent administrations. In response the company stated that, "…It is not clear to the company what 'subsequent elements of a chemotherapy cycle' means in this context and whether this refers to a type of chemotherapy where multiple elements are given within a cycle. For pembrolizumab monotherapy there are no 'subsequent elements' per cycle so it is not clear that this applies.". The EAG considers that the use of "subsequent elements of a chemotherapy cycle" is more appropriate for all IV administrations beyond the first attendance for the subsequent therapies included in the model. The EAG implemented a scenario which amended the subsequent administration costs for subsequent treatments used in the LR and DM health states to SB15Z, beyond the first administration. Due to the model structure, this was unable to be implemented for both docetaxel and vinorelbine, however as ToT is very short for these treatments, the EAG anticipates that it will not make a substantial difference.

The EAG also ran a scenario which based subsequent administration costs for pembrolizumab on the HRG code SB15Z. As these costs are applied equally in the LR and DM health state, the EAG considers that it is a conservative approach as more patients from the placebo arm will occupy these health states for a longer period of time.

Due to being previously requested by NHS England in previous technology appraisals, the EAG also implemented a scenario in which administration costs used in the model are based on the latest NHS Payment Scheme[72] as opposed to NHS Reference Costs (see Section 6).

Route	**Type of administration**	**Unit cost per administration (£)**	2021/22 NHS Reference Cost, code		
IV (simple)	Simple parenteral chemotherapy	287.00	SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance	172	SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance
IV (complex)	Complex parenteral chemotherapy	353.64	SB13Z: Deliver more Complex Parenteral Chemotherapy at First Attendance	345	SB13Z: Deliver more Complex Parenteral Chemotherapy at First Attendance
IV (subseq)	Subsequent elements of a chemotherapy cycle	368.44	SB15Z: Deliver Subsequent Elements of a Chemotherapy Cycle	345	SB15Z: Deliver Subsequent Elements of a Chemotherapy Cycle
Oral	Oral drug dispensing	216.90	SB11Z: Deliver Exclusively Oral Chemotherapy	138	SB11Z: Deliver Exclusively Oral Chemotherapy
Abbreviation: IV, intravenous;					

Disease management costs

Clinical expert advisors to the EAG stated that on progression to distant metastases they would expect all patients to receive chest radiography and that only 60% of patients would receive a PET-CT scan and 30% an MRI. Following a clarification request, the company implemented a scenario using the EAG suggested resource use for DM health state entry costs (see Section 6).

Adverse events

During the clarification process, the EAG requested that the company applied adverse event rates, durations and proportion resulting in hospitalisation by treatment arm, rather than based on pooled data. Although the company provided these data, which showed [redacted], the company did not include this in the model due to changes required to the model structure. The EAG considers that it is not a methodologically appropriate approach to pool AEs for both arms. However, as the company could not make the model changes required, they instead ran an extreme scenario in which all data on pembrolizumab AEs were used and cost of placebo AEs was set to zero. This had a small impact on the ICER.

PD-L1 test

A clinical expert to the EAG stated that PD-L1 testing is now routinely conducted in clinical practice. Therefore, the EAG requested a scenario during clarification with this removed. The company acknowledged that more centres are requesting PD-L1 testing, however it is currently determined based on the eligibility criteria for atezolizumab, which is in the CDF. The EAG recognises that the inclusion of testing is a conservative assumption. However, it is also noted by the EAG that more than one test is available to test for PD-L1 status and therefore if this cost is included, the is likely to be variability around the true cost.

End of life care

During clarification, the EAG highlighted that terminal care costs for cancer are available from the latest PSSRU Unit Costs of Health and Social Care 2022 Manual[68] and could be used as opposed to inflating previous studies on terminal care costs. The company provided a scenario analysis with the PSSRU cost used in the model upon death. The EAG consider this source to be more appropriate and is applied in the EAG base case. This is **additional issue 7** referenced in section 1.5.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Table 59 presents the cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses. The probabilistic sensitivity analysis (PSA) conducted to assess the joint parameter uncertainty around base case results used a Monte Carlo simulation and derived probabilistic results from 1,000 generated simulations. When compared to the placebo, pembrolizumab generated an additional 0.93 QALYs at an additional cost of [redacted]. The resulting probabilistic ICER was [redacted] and the deterministic ICER was [redacted].

Table 59. Company's base case results

Intervention	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental Lys	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Pembrolizumab	[redacted]	9.08	[redacted]	-	-	-	-
Placebo	[redacted]	7.98	[redacted]	[redacted]	1.10	0.93	[redacted]
Probabilistic results							
Pembrolizumab	[redacted]	9.06	[redacted]	-	-	-	-
Placebo	[redacted]	7.99	[redacted]	[redacted]	1.07	0.90	[redacted]

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

The company's PSA scatterplot is presented in Figure 23 and cost effectiveness acceptability curve (CEAC) in Figure 24. Based on the analyses, the probability that pembrolizumab is cost-effective versus placebo at both a £20,000 and £30,000 willingness to pay (WTP) threshold is [redacted] and [redacted], respectively, using the company's base case assumptions.

Figure 23. Company's PSA scatterplot, reproduced from the company's model

Figure 24. Company's cost-effectiveness acceptability curve, reproduced from the company's model

5.2 Company's sensitivity analyses

The company conducted one-way sensitivity analyses (OWSA) to assess the sensitivity of the model to individual parameter uncertainty. The company provided a tornado diagram displaying the most influential parameters on the ICER. This diagram is reproduced below based on the company's updated model.

Figure 25. OWSA tornado plot. Reproduced from the company's updated model

Abbreviations: DF, disease-free; DM, distant metastatic recurrence; local recurrence; ICER, incremental cost-effectiveness ratio; PFS, progression-free-survival; NSCLC, Non-Small Cell Lung Cancer; OS, overall survival; OWSA, one-way-sensitivity-analysis; QALY, quality adjusted life years.

5.3 Company's scenario analyses

The company undertook a range of scenario analyses to explore the impact of alternative assumptions for key model parameters. Results of the scenarios conducted by the company from the updated model are shown below in Table 60. The results shown below are based on the deterministic version of the model. As shown in the table, the ICER ranged from [redacted] (exponential/exponential DFS curves) and [redacted] (20% of DM patients on no active treatment).

Table 60. Company base case scenario analysis

Scenario	Incremental costs (£)	Incremental QALYs	Incremental LYs	ICER
Base-Case	[redacted]	0.93	1.10	[redacted]
Cure point 5 years	[redacted]	0.93	1.10	[redacted]

Cure point 5-10 years	[redacted]	0.91	1.08	[redacted]
Calibration cap 6-8 years*	[redacted]	0.96	1.15	[redacted]
Calibration removed entirely	[redacted]	0.71	0.80	[redacted]
Calibration removed, SEER-Medicare adjustment added	[redacted]	0.62	0.67	[redacted]
Calibration without SEER-Medicare adjustment*	[redacted]	0.92	1.09	[redacted]
Pembrolizumab given Q6W	[redacted]	0.93	1.10	[redacted]
Exponential/log-normal DFS curves	[redacted]	0.93	1.10	[redacted]
Weibull/log-normal DFS curves	[redacted]	0.88	1.05	[redacted]
Log-logistic/log-normal DFS curves	[redacted]	0.92	1.09	[redacted]
Gamma/log-normal DFS curves	[redacted]	0.90	1.07	[redacted]
Approach #2 Gompertz/Weibull DFS curves	[redacted]	0.99	1.17	[redacted]
Approach #3 Exponential/Exponential DFS Curves	[redacted]	1.19	1.41	[redacted]
20% of DM patients on no active treatment*	[redacted]	0.92	1.09	[redacted]
DF utilities including g1-2 Aes	[redacted]	0.87	1.10	[redacted]
G3+ AE disutilities excluded	[redacted]	0.93	1.10	[redacted]
100% cure assumption	[redacted]	0.93	1.10	[redacted]
RDI included with full KM	[redacted]	0.93	1.10	[redacted]

*The EAG notes that for this scenario the company reapplied the calibration

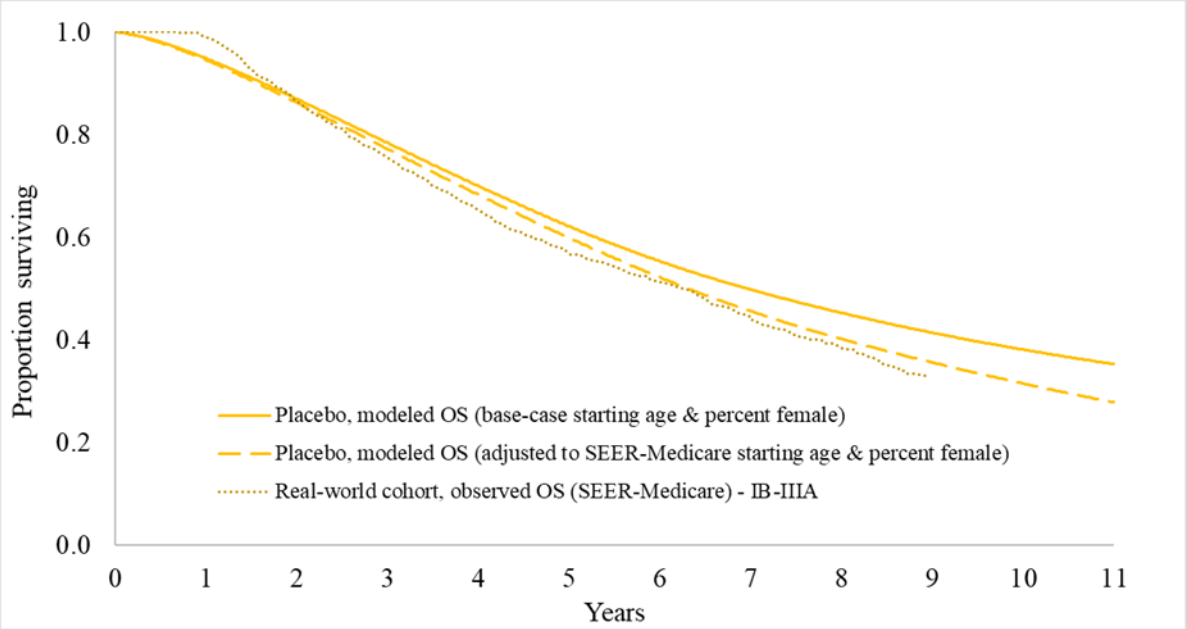
Abbreviations: AE, adverse event; DM, distant metastases; DFS, disease free survival; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LY, life-years; RDI, relative dose intensity; Q6W, every 6 weeks.

5.4 Model validation and face validity check

The long-term recurrence rate has now been validated against Sonoda *et al.* 2019[58] at clarification, as explained in section 4.2.5.1.5. However, as previously stated, this paper was found by the EAG and it is possible given an SLR there may be more appropriate sources of information to validate against.

Overall survival was validated against real-world observed data from SEER-Medicare. When age and percent female was aligned in the model with the SEER-Medicare cohort the curves of OS appeared to align as seen in Figure 26.

Figure 26. Modelled placebo OS compared with Real-world Evidence from SEER-Medicare (copy of figure 21 from CS)



Abbreviations: SEER-Medicare, The Surveillance, Epidemiology, and End Results; Non-Small Cell Lung Cancer; OS, overall survival.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The External Assessment Group (EAG) identified 2 errors in the model:

1. Following additional clarification questions, the company incorrectly updated the number of CT scans per year in the LR health state. The company applied one per year to 82% of patients. The EAG corrected this to 4 per year to 82% of patients, based on TA823[34] used to inform this resource (Section 4.2.7.3).

2. The company failed to update resource use for CT scans in the DF health state from years 5 onwards, despite stating that this was updated during clarification. The EAG corrected this error in their updated base case to include yearly scans after 5 years only (Section 4.2.7.3).

Results for these two errors are presented in Table 61.

Table 61. Corrected company base case results

	Results per patient	Pembrolizumab	Placebo	Incremental value
Company's base case post clarification				
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
Company's corrected base case post clarification				
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year;

6.2 EAG scenario analysis results

Table 62 presents the results of the company's scenario analyses in response to EAG clarification questions and EAG exploratory analyses. Results reported include the company's proposed patient access scheme (PAS) discount on the list price of [redacted]. Confidential PAS discounts or confidential medicine unit (CMU) prices are available for subsequent lines of Keytruda® (pembrolizumab), Tecentriq® (atezolizumab), bevacizumab (biosimilar), Tagrisso® (osimertinib), Alimta® (pemetrexed). As a result, the EAG has produced a confidential appendix to the EAG report. Analyses in the

confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

The EAG notes that all results shown below in Table 62 are conducted deterministically. Some results involved rerunning the calibration calculation as they impact the relationship between the OS modelled and that observed in the trial. Some of the scenarios added as company response to CQs were calculated by the EAG but requested at CQ.

Pembrolizumab was cost-effective versus placebo in all scenarios presented aside from using the individual "better fitting" DFS curves and assuming differential cure points in line with TA761 and TA823. This demonstrates the significance of the long-term benefit received from pembrolizumab in the model in determining cost-effectiveness.

Table 62. Results of the EAG's scenario analyses, deterministic

	Results per patient	Pembrolizumab	Placebo	Incremental value
0	**Company corrected base case post clarification**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
Company scenarios in response to EAG clarification questions				
B1	Baseline characteristics from the PD-L1 <50% TPS subpopulation†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B2*	Using baseline age from SEER-Medicare†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B4	Treatment effect equalised at 5 years			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B7	3-year cutpoint (best fitting) †			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B10	SMR 1.5†			
	Total costs (£)	[redacted]	[redacted]	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B11*	Using Impower010 in place of SEER-Medicare for LR transitions (Nakamichi 2017, CRT and RT (TA823))†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B15*	No re-treatment with pembrolizumab†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
B19	Q6W dosing for pembrolizumab in adjuvant and metastatic setting			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B26*	NHS payment scheme 2023/25 administration costs + HRG code SB15Z for all subsequent IV simple and complex administrations.			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B27*	Use lowest available eMIT costs			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B30	2nd line DM; Docetaxel 60%, no active treatment 40%			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B34	Alternative AE hospitalisation pemb arm			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B34	Alternative AE hospitalisation placebo arm			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B40	AEs not requiring hospitalisation costed using outpatient cost associated with AE			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]

B42	PD-L1 test costs excluded			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
EAG scenarios				
1	Baseline age changed to 68.4†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
2	Q6W dosing for 75% of pembrolizumab patients			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
3	DFS curves with improved fit; exponential/lognormal for LR/DM pembrolizumab patients and generalised-gamma/gompertz for LR/DM placebo patients†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
4	Remove ramping (cure point 7 years) †			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
5	Differential cure point (7 years for pembrolizumab 5 years for placebo) †			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
6	I/O ineligible patients not calibrated†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
7	Full KM for ToT			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
8	PSSRU end of life cost			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
9	DF utility includes grade 1 and 2 AEs			

	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]

*The company declined to provide these scenarios when requested at the clarification stage and so these have been performed by the EAG

†Recalibration was run on these model results

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year;

6.3 EAG preferred assumptions

In this section, the EAG presents its preferred analysis for the cost-effectiveness of pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer. The assumptions that form the EAG's preferred base case are listed below, with results shown in Table 63. Recalculation of the calibration factor was only performed in the final EAG base case.

1. PD-L1 <50% subpopulation baseline characteristics used; values can be found in Table 33 (**Additional issue 1**);
2. Age and percentage female varied in the PSA, this does not impact base case results (**Additional issue 2**)
3. Baseline age changed to 68.4* **(Key issue 2)**;
4. Q6W dosing for 75% of pembrolizumab patients **(additional issue 3);**
5. DFS curves with improved fit; exponential/lognormal for LR/DM pembrolizumab patients and generalised-gamma/gompertz for LR/DM placebo patients **(Key issue 3)**;
6. Calibration to match trial overall survival limited to 5 years **(Key issue 5)**;
7. I/O ineligible patients not calibrated **(Key issue 6)**;
8. Full KM for ToT **(additional issue 4);**
9. Alternative 2nd line distant metastatic treatment costs **(additional issue 5);**
10. PSSRU end of life cost **(additional issue 6);**
11. DF utility includes grade 1 and 2 AEs **(Key issue 7)**;

***Note that any calibration will need to be performed with the trial age in and then the preferred age will be reinputted, since deviation from trial OS for a higher age would be expected.**

Table 63. EAG preferred model assumptions

Preferred assumption	Section in EAG report	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
Company base case post clarification		[redacted]	[redacted]	[redacted]
PD-L1 <50% subpopulation baseline characteristics used	Section 4.2.2.1	[redacted]	[redacted]	[redacted]
Baseline age 68.4	Section 4.2.2.1	[redacted]	[redacted]	[redacted]
Q6W dosing for 75% of pembrolizumab patients	Section 4.2.3.1	[redacted]	[redacted]	[redacted]
DFS for pemb = exp/log-normal DFS for placebo = gengam/gomp	Section 4.2.5.1.5	[redacted]	[redacted]	[redacted]
Calibration limited to 5 years	Section 4.2.5.3.2	[redacted]	[redacted]	[redacted]
I/O ineligible patients not calibrated	Section 4.2.5.3.2	[redacted]	[redacted]	[redacted]
Full KM for ToT	Section 4.2.7.7	[redacted]	[redacted]	[redacted]
Alternative 2nd line distant metastatic treatment costs	Section 4.2.7.7	[redacted]	[redacted]	[redacted]
PSSRU end of life cost	Section 4.2.7.7	[redacted]	[redacted]	[redacted]
DF utility include grade 1 and 2 AEs	Section 4.2.6.4	[redacted]	[redacted]	[redacted]
Recalibration		[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; DFS, disease free survival; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; I/O, immunotherapy; KM, Kaplan Meir; QALY, quality-adjusted life-year; ToT, time on treatment.

6.3.1 EAG sensitivity analysis

The EAG's PSA scatterplot is presented in Figure 27 and cost effectiveness acceptability curve (CEAC) in Figure 24. Based on the analyses, the probability that pembrolizumab is cost-effective versus placebo at both a £20,000 and £30,000 willingness to pay (WTP) threshold is [redacted] and [redacted], respectively, using the EAG's base case assumptions.

Figure 27. EAG's base case PSA scatterplot

Figure 28. EAG's base case cost-effectiveness acceptability curve

The EAG conducted one-way sensitivity analyses (OWSA) to assess the sensitivity of the model to individual parameter uncertainty.

Figure 29. OWSA tornado plot. Produced from EAG's base case model

Abbreviations: DF, disease-free; DM, distant metastatic recurrence; local recurrence; ICER, incremental cost-effectiveness ratio; PFS, progression-free-survival; NSCLC, Non-Small Cell Lung Cancer; OS, overall survival; OWSA, one-way-sensitivity-analysis; QALY, quality adjusted life years.

6.4 EAG additional analysis

The following additional sensitivity analyses were also undertaken using the ERG's preferred analysis to explore the sensitivity to alternative assumptions.

- 100% dosing Q6W for pembrolizumab (adjuvant and post-recurrence);
- Generalised gamma DF to LR pembrolizumab;
- Cure 7 years (no ramping);
- Differential cure point 5 years for placebo 7 for pembrolizumab;
- Alternatives to SEER-Medicare LR transition (recalibration);
- Equalise pembrolizumab and placebo after 7 years;
- Remove calibration.

As shown in Table 64, in all analyses the ICER for pembrolizumab compared to placebo was above a willingness to pay threshold of £30,000.

Table 64. EAG additional sensitivity analyses, applied to the EAG preferred base case analysis

	Results per patient	Pembrolizumab	Placebo	Incremental value
0	**EAG preferred analysis**			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
1	100% Q6W			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
2	Gen gamma DF to LR pembrolizumab;			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
3	Cure 7 years (no ramping)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
4	Differential cure point 5 years for placebo 7 for pembrolizumab			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
5	Alternatives to SEER-Medicare LR transition (recalibration)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
6	Equalise pembrolizumab and placebo after 7 years			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
7	Remove calibration (include graph).			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year;

6.5 Conclusions of the cost effectiveness sections

The cost-effectiveness results presented in this submission are heavily reliant on assumptions surrounding the modelling of disease-free survival (DFS) and to a lesser extent recurred patients. Changing DFS alone results in an ICER higher than the upper threshold typically used by NICE in Single Technology Appraisals (£30,000 per QALY gained). It is important to acknowledge that while the EAG has justified the use of its preferred curves by suggesting that there is a waning effect, no waning effect is implemented in the model. The best-fitting parametric curves, if used, naturally show pembrolizumab disease-free-survival trending towards placebo shortly after 5 years. In the company base case, significant long-term benefit (past 20 years) is derived from their worse fitting model. Mean square error was lower for the EAG preferred curve fir pembrolizumab compared to the company's preferred curve (0.0001686 versus 0.0002097) and for the EAG's preferred curve for placebo compared to the company's preferred curve (0.0001876 versus 0.0007512).

It is also worth emphasizing that this approach to the long-term uncertainty is not unique to this appraisal. TA761 and TA823 both assumed differential cure points into their base case to address uncertainties in the expectation of post-trial DFS data. If this appraisal were to take a similar approach it would have a comparable impact to these alternate curves, as demonstrated by the scenario analysis in Table 62.

The other major issue that could impact cost-effectiveness is the significant uncertainty surrounding trajectory of patients post-recurrence. The calibration used by the company, already serves as an imprecise way of aligning with the trial data as it applies a single multiplier to all transitions assuming the benefit from pembrolizumab is not time-dependent and distributed evenly across local and distant metastatic recurrence. However, this is stacked on top of a combination of registry and trial data for local and distant metastatic recurrence, which is assumed to be best fit with an exponential model. These assumptions do not inherently favour pembrolizumab over placebo but they are likely to be inaccurate and so introduce significant uncertainty. The EAG did test removing calibration in the base case to see if the uncalibrated EAG base case resulted in any closer fit to trial OS, however, as demonstrated in Figure 30 and Figure 31, the pembrolizumab arm still required adjustment to match the trial OS.

Figure 30. Uncalibrated OS EAG base case

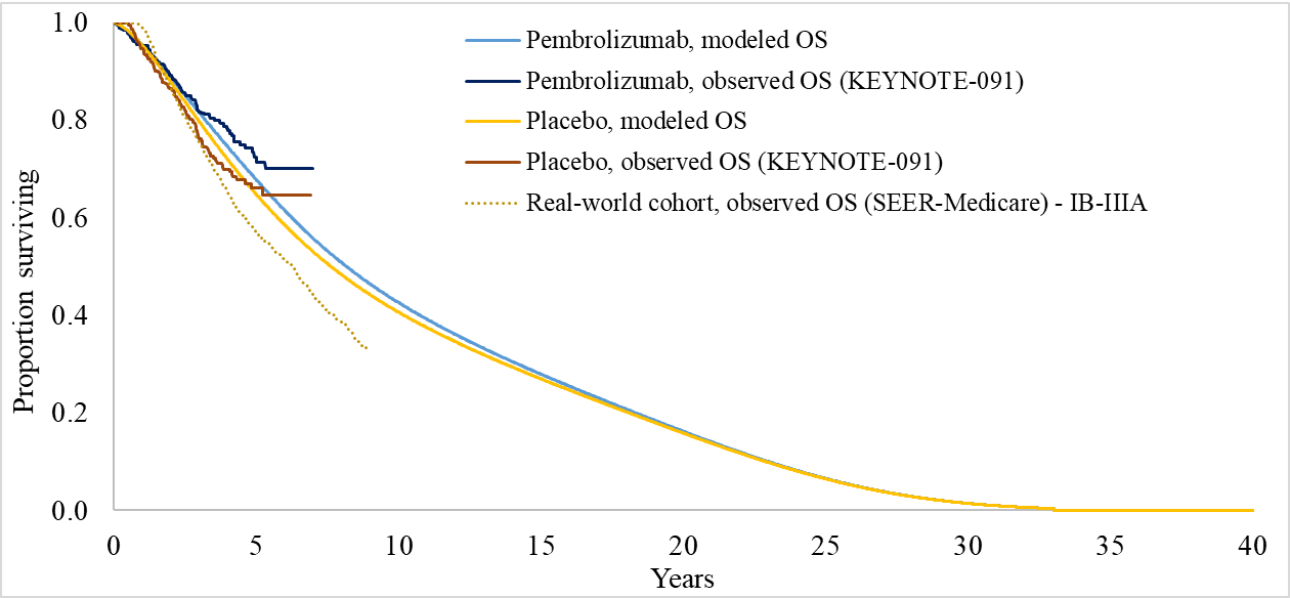
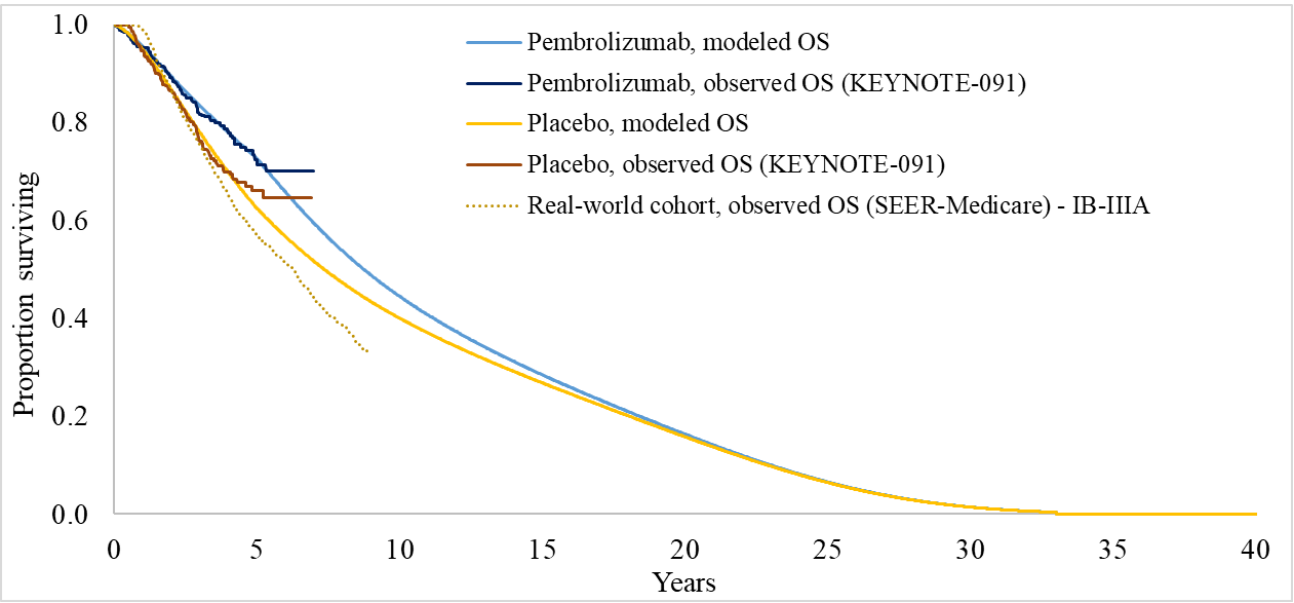


Figure 31. Calibrated OS EAG base case



Based on the available evidence, at the current discounted price, the ICER for pembrolizumab versus placebo is higher than the upper threshold typically used by NICE in Single Technology Appraisals (£30,000 per QALY gained).

7 References

1. Digital NHS. Cancer Survival in England, cancers diagnosed 2016 to 2020, followed up to 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-survival-in-england/cancers-diagnosed-2016-to-2020-followed-up-to-2021 [Access Date: 25 February 2024]. 2023.
2. UK CR. Lung Cancer statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-One. Date accessed: 09 April 2024.
3. Cancer Research UK. Types of lung cancer. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types. Date accessed: 9 April 2024.
4. Non-Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version. Available from: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq. Date accessed: 09 April 2024.
5. Cancer Research UK. Lung cancer risk. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/risk-factors#ref-19. [Access Date: 25 February 2024].
6. National Lung Cancer A. National Lung Cancer Audit (NLCA) – State of the nation report 2023 for patients in England during 2021 and Wales during 2020-2021. Available from: https://www.hqip.org.uk/resource/lung-cancer-ncla-apr23/ . [Access Date: 25 February 2024]. 2023.
7. NHS. Overview. Lung cancer. Available from: https://www.nhs.uk/conditions/lung-cancer/. Date accessed: 09 April 2024.
8. UK CR. Lung cancer incidence statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-Zero. Date accessed: 09 April 2024.
9. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. *Chest* 2017; **151**: 193-203.
10. Tsim S, O'Dowd CA, Milroy R, Davidson S. Staging of non-small cell lung cancer (NSCLC): a review. *Respiratory medicine* 2010; **104**: 1767-74.
11. Lababede O, Meziane MA. The Eighth Edition of TNM Staging of Lung Cancer: Reference Chart and Diagrams. *The oncologist* 2018; **23**: 844-8.
12. Mirsadraee S, Oswal D, Alizadeh Y, Caulo A, van Beek E, Jr. The 7th lung cancer TNM classification and staging system: Review of the changes and implications. *World J Radiol* 2012; **4**: 128-34.
13. Sugimura H, Nichols FC, Yang P, Allen MS, Cassivi SD, Deschamps C, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. *Ann Thorac Surg* 2007; **83**: 409-17; discussioin 17-8.
14. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008; **26**: 3552-9.
15. Chouaid C, Danson S, Andreas S, Siakpere O, Benjamin L, Ehness R, et al. Adjuvant treatment patterns and outcomes in patients with stage IB-IIIA non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. *Lung cancer (Amsterdam, Netherlands)* 2018; **124**: 310-6.
16. National Institute for H, Care E. Quality standard [QS17] - Lung cancer in adults. 2019.
17. Osarogiagbon RU, Lin CC, Smeltzer MP, Jemal A. Prevalence, Prognostic Implications, and Survival Modulators of Incompletely Resected Non-Small Cell Lung Cancer in the U.S. National Cancer Data Base. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2016; **11**: e5-16.

18. Felip E, Altorki N, Zhou C, Vallieres E, Martinez-Marti A, Rittmeyer A, et al. Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial. *Annals of oncology : official journal of the European Society for Medical Oncology* 2023; **34**: 907-19.
19. Medicines, Healthcare products Regulatory A. KEYTRUDA® Summary of Product Characteristics. Available from: https://products.mhra.gov.uk/search/?search=keytruda&page=1 [Access Date: 21 February 2024].
20. European Medicines A. EMEA/H/C/003820/II/0121. Keytruda European Public Assessment Report (EPAR). Available from: https://www.ema.europa.eu/documents/variation-report/keytruda-h-c-003820-ii-0121-epar-assessment-report-variation_en.pdf. 2023.
21. National Institute for Health and Care Excellence (NICE). ID6220 - Durvalumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11197.
22. National Institute for Health and Care Excellence (NICE). TA823 Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta823 . 2022.
23. National Institute for Health and Care Excellence (NICE). TA761 Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection. Available from: https://www.nice.org.uk/guidance/ta761. 2022.
24. Peters S, Reck M, Smit EF, Mok T, Hellmann M. How to make the best use of immunotherapy as first-line treatment of advanced/metastatic non-small-cell lung cancer. *Annals of oncology* 2019; **30**: 884-96.
25. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol* 2022; **23**: 1274-86.
26. Oselin K, Shim BY, Okada M, Bryl M, Bonanno L, Demirag G, et al. Pembrolizumab vs placebo for early-stage non–small-cell lung cancer after resection and adjuvant therapy: Subgroup analysis of patients who received adjuvant chemotherapy in the phase 3 PEARLS/KEYNOTE-091 study. *Journal of Clinical Oncology* 2023; **41**: 8520-.
27. National Institute for Health and Care Excellence. Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907] Final Scope. 2024. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10784/documents. Date accessed: April 2024.
28. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898.
29. Higgins Jpt SJPMJERGSJAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.
30. Belot A, Fowler H, Njagi EN, luque-Fernandez M-A, Maringe C, magadi W, et al. Association between age, deprivation and specific comorbid conditions and the receipt of major surgery in patients with non-small cell lung cancer in England: A population-based study. *Thorax* 2024; **74**.
31. Msd. Data on File. KEYNOTE-091 Clinical Study Protocol.
32. Msd. Data on File. KEYNOTE-091 IA3 Statistical Report.
33. Msd. Data on File. KEYNOTE-091 IA3 Clinical Study Report.
34. National Institute for H, Care E. TA823 Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta823. 2022.
35. Scottish Medicines C. SMC2492 - Atezolizumab 840mg and 1,200mg concentrate for solution for infusion (Tecentriq®). Detailed Advice Document. Available from:

https://www.scottishmedicines.org.uk/media/7043/atezolizumab-tecentriq-final-july-2022-amended-130722-for-website.pdf. [Access Date: 27 October 2023].
36. National Institute for H, Care E. TA761 Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection. Available from: https://www.nice.org.uk/guidance/ta761. 2022.
37. Scottish Medicines C. SMC2383 - Osimertinib 40mg and 80mg film-coated tablets (Tagrisso®). Detailed Advice Document. Available from: https://www.scottishmedicines.org.uk/media/6422/osimertinib-tagrisso-final-october-2021-for-website.pdf. [Access Date: 29 February 2024].
38. National Institute for H, Care E. NICE guideline [NG122]. Lung cancer: diagnosis and management. Full guideline (2011). Last updated: 26 July 2023. Available from: https://www.nice.org.uk/guidance/ng122/evidence/full-guideline-pdf-6722113502. 2023.
39. National Institute for H, Care E. TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer. Available from: https://www.nice.org.uk/guidance/ta181. 2009.
40. National Institutes of H. SEER data 2007-2017 - Medicare claims data: 2007-2019. Available from: https://healthcaredelivery.cancer.gov/seermedicare.
41. Reck M, Srivastava MK, Wakelee HA, Felip E, Altorki NK, Csoszi T, et al. IMpower010: Exploratory Analysis of Disease-Free Survival By KRAS Status In Patients With Stage II-IIIA NSCLC Treated With Adjuvant Atezolizumab Vs Best Supportive Care. 2023. p. American Society of Clinical Oncology Annual Meeting 2023.
42. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *The New England journal of medicine* 2022; **386**: 1973-85.
43. Wakelee H, Liberman M, Kato T, Tsuboi M, Lee SH, Gao S, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. *The New England journal of medicine* 2023; **389**: 491-503.
44. Ball Jessica GA, Charles Comins, Adam Dangoor, Helen Brooks, Waheeda Owadally,. 77 Toxicity and outcomes for patients with resected Non-Small cell lung cancer (NSCLC) who have received adjuvant chemotherapy in Bristol,
Lung Cancer. 2024; **190**.
45. Belcher E, Mitchell J, Stavroulias D, Di Chiara F, Rahman N. Optimal resection rate for lung cancer in the UK: how high should we go? *BMJ Open Respir Res* 2021; **8**.
46. Belot A, Fowler H, Njagi EN, Luque-Fernandez M-A, Maringe C, Magadi W, et al. Association between age, deprivation and specific comorbid conditions and the receipt of major surgery in patients with non-small cell lung cancer in England: A population-based study. *Thorax* 2019; **74**: 51-9.
47. Office for National S. National life tables: UK. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. [Last accessed: 05/02/3034].
48. 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**: 1505-17.
49. Novello S, Kowalski DM, Luft A, Gümüş M, Vicente D, Mazières J, et al. Pembrolizumab Plus Chemotherapy in Squamous Non–Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. *Journal of Clinical Oncology* 2023; **41**: 1999-2006.
50. National Institute for H, Care E. TA766 Pembrolizumab for adjuvant treatment of completely resected stage 3 melanoma. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta766/documents/committee-papers. [Access Date: 29 February 2024]. 2022.
51. National Institute for H, Care E. TA837 Pembrolizumab for adjuvant treatment of resected stage 2B or 2C melanoma. Committee Papers. Available from:

https://www.nice.org.uk/guidance/ta837/documents/committee-papers. [Access Date: 29 February 2024]. 2022.
52. National Institute for H, Care E. TA851 Pembrolizumab for neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer. Committee Papers. Available from: https://www.nice.org.uk/guidance/ta851/documents/committee-papers. [Access Date: 29 February 2024]. 2022.
53. National Institute for H, Care E. Pembrolizumab for adjuvant treatment of renal cell carcinoma. Available from: https://www.nice.org.uk/guidance/ta830. 2022.
54. Latimer N. NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA. Last Updated: March 2013. Available from: https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD14-Survival-analysis.updated-March-2013.v2.pdf. [Access Date: 29 February 2024]. 2013.
55. *Principles and practice of clinical research*. Washington, WA: Elsevier; 2017.
56. National Institute for H, Care E. TA569 Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer. Committee Papers. Available from: https://www.nice.org.uk/guidance/TA569. [Access Date: 05 March 2024]. 2019.
57. Takeuchi H, Muto Y, Tashiro H. Clinicopathological characteristics of recurrence more than 10 years after surgery in patients with breast carcinoma. *Anticancer Res* 2009; **29**: 3445-8.
58. Sonoda D, Matsuura Y, Ichinose J, Nakao M, Ninomiya H, Mun M, et al. Ultra-late recurrence of non-small cell lung cancer over 10 years after curative resection. *Cancer Manag Res* 2019; **11**: 6765-74.
59. West H, Hu X, Zhang S, Song Y, Chirovsky D, Gao C, et al. Evaluation of disease-free survival as a predictor of overall survival and assessment of real-world burden of disease recurrence in resected early-stage non-small cell lung cancer. *J Manag Care Spec Pharm* 2023; **29**: 749-57.
60. MSD. Data on File. Early-stage non-small cell lung cancer (NSCLC) Clinical Advisory Board meeting. July 2022.
61. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. *The New England journal of medicine* 2020; **382**: 41-50.
62. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med* 2018; **378**: 113-25.
63. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2010; **13**: 509-18.
64. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. NICE DSU Report. 2022.
65. NHS Business Services Authority (NHSBSA). Electronic Drug Tariff Database. 2024. Available from: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff. Date accessed.
66. National Institute for H, Care E. TA939 Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer. Available from: https://www.nice.org.uk/guidance/ta939. [Access Date: 29 February 2024]. 2023.
67. England N. NHS Reference Costs. 2021/22 National Cost Collection Data Publication. Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/. [Access Date: 29 February 2024].
68. Personal Social Services Research U. Unit Costs of Health and Social Care programme (2022 – 2027). Available from: https://www.pssru.ac.uk/unitcostsreport/. [Access Date: 29 February 2024].

69. Georghiou T, Bardsley M. Exploring the cost of care at the end of life. Research report [Internet]. Nuffield Trust. Available from: https://www.nuffieldtrust.org.uk/research/exploring-the-cost-of-care-at-the-end-of-life. 2014.
70. Administration FaD. Navelbine. FULL PRESCRIBING INFORMATION. 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020388s037lbl.pdf. Date accessed.
71. England N. Cisplatin and Vinorelbine and radiotherapy (NSCLC). 2018. Available from: https://www.england.nhs.uk/south/wp-content/uploads/sites/6/2018/11/Cis-vin-radv2-1.pdf. Date accessed.
72. 2023-25 NHS Payment Scheme (amended) [Internet]. 2024. Available from: https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/.

8 Appendices

8.1 Price sources for treatments included in the confidential appendix

The table below shows the source of confidential prices used in the cPAS appendix. In addition to commercial arrangements, the EAG also updated prices available from the latest version of eMIT (April 2024) and applied the cheapest dose available.

Table 65. Source of the confidential prices used in the confidential appendix

Treatment	Source
Osimertinib	CAA
Pembrolizumab (for untreated PD-L1-positive metastatic NSCLC)	CAA
Pembrolizumab (with carboplatin and paclitaxel)	CAA
Pembrolizumab (with pemetrexed and platinum chemotherapy)	CAA
Pemetrexed	CMU
Carboplatin	eMIT
Cisplatin	eMIT
Docetaxel	eMIT
Paclitaxel	eMIT
Vinorelbine	eMIT

Abbreviations: CAA, commercial access arrangement; CMU, commercial medicines unit; eMIT, Drugs and pharmaceutical electronic market information tool; PAS, patient access scheme.

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

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 Monday 3 June** 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 [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Clarity on the target population not being a pre-specified subgroup

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 3 (page 20): "The EAG notes that the target population for this appraisal was not a prespecified subgroup in the KEYNOTE-091 trial".	The following amendment in bold is suggested: "The EAG notes that the target population for this appraisal was not a prespecified subgroup in the KEYNOTE-091 trial, **whereas the PD-L1 TPS 0% and 1-49% were pre-specified subgroups and stratification factors**."	While it is acknowledged that that the target population is not a prespecified subgroup of the KEYNOTE-091 trial, it should be made clearer that this subpopulation combines the pre-specified 0% and 1-49% subgroups which are stratification factors. This would suggest greater validity of the results in this subpopulation and greater credibility compared to a completely ad-hoc subgroup.	The EAG thanks the company and has amended the wording of this sentence to read: "**The EAG notes that although the PD-L1 TPS 0% and 1-49% were prespecified subgroups and stratification factors in the KEYNOTE-091 trial, the target population for this appraisal was not a prespecified subgroup in the KEYNOTE-091 trial.''**

Issue 2 Impact of smaller subpopulation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 3 (page 20): "..the EAG notes that, as a result of focusing on a smaller subpopulation of the original sample required for the	It should be made clearer that the smaller sample size of the subpopulation may result in a reduced power, rather than an increase in the risk of Type I error.	The smaller sample size does not inherently increase the Type I error rate, which is determined by the pre-specified significance level.	Not a factual inaccuracy. The EAG considers that the possibility of focusing on a subpopulation from the original sample

study to have sufficient power, *results for the PD-L1 TPS <50% subpopulation are at risk of Type I error and so could be due to chance*"			being, at least partially, a data-driven decision cannot be ruled out and thus at risk of a Type I error.

Issue 3 Description of treatment waning assumption

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 5 (page 22): "In the pembrolizumab arm, *there is significant evidence of treatment waning,* which is not accounted for using the company's model selection" **Table 5 (page 22)**: "Treatment waning has previously accepted for adjuvant treatment of renal cell carcinoma (TA830)." **Table 5 (page 22)**: "*Correcting this issue* significantly decreases the	It is suggested that "**the EAG believes**" should be inserted to reflect the EAG's position on this topic. It should be made clearer that the treatment waning previously accepted was based on the assumptions after the observed follow-up time as opposed to the available evidence. The following amendment is suggested: "**The use of the EAG's preferred**	As there is no obvious evidence supporting the treatment waning, considering the uncertainties when interpreting the KM curves at later time points, it should be made clearer that this represents EAG's view and it is not fully established.	These is not a factual inaccuracy. However, the following changes have been made: **Table 5 (page 22)**: "Treatment waning has previously **been** accepted for adjuvant treatment of renal cell carcinoma (TA830)." "**The use of the EAG's preferred assumption** significantly decreases the cost-effectiveness of

cost-effectiveness of pembrolizumab compared to placebo." **Section 4.2.5.1.5 (page 95)**: "As a result of *this evidence of waning*, the EAG's position is that the proportional hazards assumption is potentially violated." **Section 4.2.5.1.5 (page 96)**: "The EAG considers the improved fit from these preferences along with the *observed treatment waning* constitutes the strong evidence required for using different model types for each arm." Section 4.2.5.3.2 (page 106): "As suggested by the EAG in section 4.2.5.1.5, there *is evidence of treatment effect waning* in	**assumption** significantly decreases the cost-effectiveness of pembrolizumab compared to placebo." The following amendment is suggested: " As a result of this evidence of **potential** waning, the EAG's position is that the proportional hazards assumption is potentially violated." The following amendment is suggested: "The EAG considers the improved fit from these preferences along with ~~the~~ **a numerical narrowing of hazards at late time points in the KM curves when the majority of patients have been administratively censored** ~~observed treatment waning~~ constitutes the strong evidence required for using different model types for each arm." The following amendment is suggested: "As suggested by the EAG in section 4.2.5.1.5, **the EAG believe** there is **some** evidence of treatment effect		pembrolizumab compared to placebo." No other corrections here have been accepted. It should be noted that the company have inaccurately portrayed the evidence of waning as "**a numerical narrowing of hazards at late time points in the KM curves when the majority of patients have been administratively censored**" This narrowing begins to be seen between 18 and 24 months whereas it is not till month 36 where the majority of patients are censored.

the disease-free survival curves”	waning in the disease-free survival curves”		

Issue 4 Rationale for company’s proposed positioning

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2.1 (page 30): “The company positions pembrolizumab in clinical practice, in the subpopulation with PD-L1 biomarker expression with less than 50% TPS. This is in line with the results of the phase 3 KEYNOTE-091 trial informing the current submission, which demonstrate greater effectiveness in the PDL-1 TPS <50% subpopulation. “	It is suggested the following text be added: “**It also reflects the population in the adjuvant setting with higher unmet medical need with no adjuvant treatment options beyond chemotherapy available** “	For completeness, it should be added that the proposed positioning, in addition to be in line with the greater benefits demonstrated in this subpopulation, also reflects the population with higher unmet medical need.	This has been added to the EAG report.

Issue 5 Minor correction: KEYNOTE-091 terminology

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.31 (page 41): "In the economic model, the baseline characteristics of patients were based on the overall KEYNOTE-*019* trial population."	The correct trial name is KEYNOTE-091.	Justify why the error needs correcting and the impact it will have	The EAG thanks the company for identifying this and has amended the report.

Issue 6 Rationale for pembrolizumab positioning

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2 (page 48): "That is because it could be a data-driven decision, potentially overestimating the effectiveness of pembrolizumab over placebo as, as stated in the CS, this population reflects where pembrolizumab provides the most clinical benefit in the adjuvant setting".	The following text is suggested: "**The company stated in the CS that the proposed positioning reflects the subpopulation in the adjuvant setting with a substantial unmet need whose clinical benefits associated with pembrolizumab are supported by more robust evidence**."	For completeness it should be added that the company's rationale for the proposed positioning is that clinical benefits associated with pembrolizumab in this subpopulation are those supported by robust evidence, as opposed to the evidence in the PD-L1 TPS > 50% whose uncertainties	Not a factual inaccuracy. The EAG notes the following sentence in the same paragraph conveys this: 'The company also noted that the choice to focus on the PD-L1 TPS <50% subpopulation was not data-driven but reflects the population in the adjuvant setting with no adjuvant treatment options beyond

		would limit the use of pembrolizumab in this group.	chemotherapy available with a high unmet medical need.'

Issue 7 Definition of DFS vs EFS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3 (page 53): "They noted that looking at DFS rather than EFS avoids looking at events occurring *after* surgery [..]".	It should read "**before**" surgery.	DFS does not consider events happening prior to potential surgery (e.g., progression of disease precluding surgery and inability to resect the tumour).	The EAG thanks the company for identifying this and has amended the report.

Issue 8 Clarity on the subpopulation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3.3 (page 64): "*The PD-L1 TPS subpopulation* was not a pre-specified efficacy population in the	It is suggested that more details be added on the PD-L1 TPS subpopulation that was not a pre-specified efficacy population as follows: "The PD-L1 TPS **< 50%**	This would provide more clarity as other PD-L1 subgroups are pre-specified	The EAG thanks the company for identifying this and has amended the report.

KEYNOTE-091 trial and […]."	subpopulation was not a pre-specified efficacy population in the KEYNOTE-091 trial and […]."	subgroups in the efficacy analyses.	

Issue 9 Minor correction: p-value for EQ-5D-3L Utility Score

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3.6 (page 71) provides the wrong p-value ([redacted]) for the EQ-5D-3L Utility Score.	The correct p-value is [redacted].	Justify why the error needs correcting and the impact it will have	The EAG thanks the company for identifying this and has amended the report.

Issue 10 Description of AEs leading to death

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3.6 (page 73): "[..] of the deaths in pembrolizumab and none of the deaths in the placebo group were due *to AEs* […]"	It is suggested that the following text in bold be added to explain that the sentence refers to drug-related AEs: "[..] of the deaths in pembrolizumab and none of the deaths in the placebo group were due to AEs **considered to**	Justify why the error needs correcting and the impact it will have	The EAG thanks the company for identifying this and has amended the report.

	be drug-related by the investigator […]”		

Issue 11 Minor correction: Trial number

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In **section 3.5 (page 76)** the trial number reported (*NCT02504272*) is not correct.	The correct trial number is **NCT02504372**.	Justify why the error needs correcting and the impact it will have	The EAG thanks the company for identifying this and has amended the report.

Issue 12 Minor correction: SLR location in the CS Appendices

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.1, Table 30 (page 78), HRQoL evidence column from search strategy to data extraction’	Table 30 of the EAG report reports HRQoL evidence search strategy, inclusion/exclusion criteria, screening and data extraction as being found in Appendix H of the CS Appendices. As the SLR methodology combined the methodology for cost-effectiveness, HRQoL and costs and healthcare resource use searches these were	To accurately reflect where the SLR methodology can be found in the CS.	The EAG thanks the company for identifying this and has amended the report.

	derived from the same methodology which can be found in Appendix G. We suggest amending the search strategy, inclusion/exclusion criteria, screening and data extraction from 'Appendix H' to: 'Appendix G'		
Section 4.1, Table 30 (page 78), Resource use and costs evidence column from search strategy to data extraction'	Table 30 of the EAG report reports resource use and costs evidence search strategy, inclusion/exclusion criteria, screening and data extraction as being found in Appendix H of the CS Appendices. As the SLR methodology combined the methodology for cost-effectiveness, HRQoL and costs and healthcare resource use searches these were derived from the same methodology which can be found in Appendix G. We suggest amending the search strategy, inclusion/exclusion criteria, screening and data extraction from 'Appendix I' to: 'Appendix G'	To accurately reflect where the SLR methodology can be found in the CS.	The EAG thanks the company for identifying this and has amended the report.

Issue 13 Minor correction: definition of population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.2 (page 81): **"**For baseline characteristics the total *ITT population* was used, which [..]"	It is suggested amending the population to "**Overall population** (ITT population)".		The EAG has amended the report.

Issue 14 Minor correction: SEER-Medicare terminology

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the EAG report (pages 82, 85, 100-101, 103-106, 133, 136-137, 142-143)	"SEER" is not the correct term for this database. We suggest amending this to "SEER-Medicare"	To accurately reflect the real-world data source used for the KEYNOTE-091 submission.	The EAG thanks the company for identifying this and has amended the report.

Issue 15 Correction: number of model health states

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.4.1 (page 85) it states:	In the CS in Section B.3.2.2, the model structure is described as having "four mutually exclusive health states (i.e., disease-free, local-regional recurrence,	To accurately reflect the health states included in the model structure.	The EAG thanks the company for identifying

"…the company describes the model as consisting of five-states as DM is separated into first- and second-line for pre- and post-progression within distant metastatic patients."	distant metastases, and death) to track the disease course and survival of patients over time, although the DM state is comprised of two sub-states which reflect first and second line treatment".		this and has amended the report.

Issue 16 Minor correction: KEYNOTE-091 terminology

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.5.3.1 (page 103) "KEYNOTE-091" is referred to as "KEYNOTE-093"	KEYNOTE-091	To accurately reflect the pivotal trial name.	The EAG thanks the company for identifying this and has amended the report.

Issue 17 Minor correction: drug acquisition cost per administration of carboplatin

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7, Table 53 (pages 117-118) carboplatin drug acquisition	We suggest the carboplatin drug acquisition cost per administration to be "£29.38"	To accurately reflect the drug acquisition cost per administration for carboplatin.	The EAG thanks the company for identifying

cost per administration is described as “£29.38mg”			this and has amended the report.

Issue 18 Correction: Post clarification deterministic ICER

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.1, (page 130) the deterministic ICER was described as “[redacted]”	We suggest the deterministic ICER to be “[redacted]”	To accurately reflect the deterministic ICER presented post clarification.	The EAG thanks the company for identifying this and has amended the report.

Location of incorrect marking	Description of proposed amendment	Justification for amendment	EAG response
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.	

Section 3.2, Table 15 (page 51), row related to "dropouts"	The information below can be left unmarked as it is publicly available and was not marked in the CS. "The proportion of participants who completed study medication was lower in the pembrolizumab group ([redacted]) compared with the placebo group ([redacted]%). The most common (>15%) reasons for study medication discontinuation in the pembrolizumab group compared with the placebo group were study medication toxicity ([redacted]% vs [redacted]%, respectively) and recurrence/relapse/death due to disease progression ([redacted] vs [redacted], respectively). The proportion of the participants in each treatment arm who were ongoing in the study was similar (pembrolizumab group [[redacted]]; placebo group [[redacted]]. The most common reason for study discontinuation in the pembrolizumab group and the placebo group was death ([redacted] vs [redacted], respectively)."	"The proportion of participants who completed study medication was lower in the pembrolizumab group (51.7%) compared with the placebo group (65.6%). The most common (>15%) reasons for study medication discontinuation in the pembrolizumab group compared with the placebo group were study medication toxicity (19.7% vs 3.8%, respectively) and recurrence/relapse/death due to disease progression (12.4% vs 21.9%, respectively). The proportion of the participants in each treatment arm who were ongoing in the study was similar (pembrolizumab group [72.7%]; placebo group [70.7%]. The most common reason for study discontinuation in the pembrolizumab group and the placebo group was death (23.1% vs 26.2%, respectively)."	The EAG thanks the company for identifying this and has amended the report.

Section 3.3.6 (page 72)	The information below can be left unmarked as it is publicly available and was not marked in the CS. "The proportion of patients experiencing an AE in each group was [redacted] and [redacted] for pembrolizumab group and placebo, respectively."	"The proportion of patients experiencing an AE in each group was 95.9% and 91% for pembrolizumab group and placebo, respectively."	The EAG thanks the company for identifying this and has amended the report.
Section 4.2.5.1.5 (page 99) it states "The company scenario using an SMR of 1.5 resulted in an ICER of £23,416"	"The company scenario using an SMR of 1.5 resulted in an ICER of [redacted]"	All scenario results within the CS should be marked CIC.	The EAG thanks the company for identifying this and has amended the report.
Section 4.2.5.3.1 Figures 18 and 19 (pages 104-105) Uncalibrated and calibrated modelled OS vs observed OS were unmarked.	Uncalibrated and calibrated modelled OS vs observed OS should be marked as CIC.	OS rates over time and OS KM curve for the PD-L1<50% subpopulation are not available in the public domain.	The EAG thanks the company for identifying this and has amended the report.
Section 5.2, figure 25 (page 132), figures 27-28 (page 141), figure 29 (page 142)	The company and the EAG's OWSA tornado plots and the EAG's PSA scatterplot and CEAC are currently unmarked as CIC. We suggest these to be marked as CIC.	PSA and DSA results can be used to back calculate confidential net price of pembrolizumab.	The EAG thanks the company for identifying this and has amended the report.

Section 6.1, table 61-62 (pages 135-138), table 64 (pages 142-143)	All total costs and QALYs from the EAG's base-case and sensitivity analyses should be marked CIC and underlined as opposed to only marking the cells within the table.	Base-case results and scenario analyses can be used to back calculate confidential net price of pembrolizumab. In addition, this is in line with NICE guidance on CIC marking.	The EAG thanks the company for identifying this and has amended the report. In addition, **Table 59, Table 60, Table 63** have also been updated by removing the marking of the cells and replacing with in-text highlighting and underlining.

Dear NICE Technical Team (cc:EAG),

While the MSD team are content that the majority of changes included in the EAG's base case represent reasonable alternative interpretations of the evidence, we are very concerned about the EAG's base case DFS survival analysis selections and wish to suggest an additional or alternative set of curves is presented to the committee at ACM1, namely using generalized gamma for both DF->LR transitions and log-normal for both DF->DM transitions. Our motivation here is to try to reduce the need for a second committee meeting by presenting the committee with a credible "middle ground" between the EAG's preferences and our own.

The EAG appear to have selected the 4 DFS curve options that have the lowest AIC, but the importance of the clinical plausibility of the resulting projections in curve selection is not obviously documented in the EAG report. A summary of key issues runs as follows and is expanded upon afterwards:-

a. An exponential curve with constant hazard over time is conceptually unlikely to be appropriate for projecting recurrences in the adjuvant setting, particularly when it applies to only one arm
b. A Gompertz curve with zero hazard after the follow-up time is unlikely to be conceptually appropriate for modelling recurrences in the adjuvant setting, particularly when it applies to only one arm
c. The Overall Survival Hazard Ratio produced by the model under the EAG's curve selection is in favour of placebo from year 5 to year 26 in the model, after which point the HR=1. This is not clinically plausible.
d. The "cure point" in early NSCLC is not known precisely and, as discussed in the EAG report, a variety of assumptions have been examined in relevant NICE appraisals. If the committee are interested in sensitivity analyses where the cure takes place from 5-8 years instead of 5-7 years, for example, then DFS in the pembrolizumab arm is actually lower than the placebo arm, which would be clinically implausible.
e. The EAG's model produces "ultra-late" recurrences which are 0.18x the value discussed at Clarification Questions in the placebo arm, whereas "ultra-late" occurrences (>10 years) are 1.4x the value in the pembrolizumab arm. It is not clear why the "ultra-late" occurrence rate would be 7.5x higher in the pembrolizumab arm than in the placebo arm.
f. The use of differential distributions for the DF->LR and DF->DM transitions is contrary to guidance in TSD14. An option exists that adheres to the TSD14 guidance, while satisfying the EAG's desire for very close visual fit to the KM data and not producing clinically implausibly projections; namely using generalized-gamma for both DF->LR transitions and log-normal for both DF->DM transitions.
g. The EAG is modelling pembrolizumab to have zero curative advantage; the only benefit being a delay in recurrences. This is contrary to advice received at the MSD 2023 UK advisory board where clinicians confirmed that the company's model including a differential proportion of cured patients was plausible.
h. The company considers that the EAG's interpretation that there is evidence of treatment waning in KEYNOTE-091 is not supported by the evidence. The gap between the curves only meaningfully narrows after 4 years, when approximately 2/3 of remaining DFS patients have been administratively censored (patients are only routinely followed up once per year at this point in the trial and therefore any

asymptomatic recurrences will only be discovered at yearly follow-up). Very few events occur after 4 years (5 in the placebo arm and 14 in the pembrolizumab arm), compared to over 300 DFS patients, 2/3 of whom have been censored.

i. Maintaining all the EAG's base case settings and selecting the generalised-gamma/log-normal curves in both arms results in an ICER of approximately £[redacted]/QALY gained. The company consider this to be a much more reasonable conservative alternative to the base case than the approach presented in the EAG report.

<u>The exponential curve is likely inappropriate</u>

Exponential curves have the property of constant hazards with respect to time. This conceptually makes little sense in the adjuvant setting, where the denominator comprises an ever-growing proportion of patients who are genuinely cured. The risk of recurrence must reduce over time, by definition. While the exponential model has very slightly lower AIC (1-2 points, which is not statistically meaningful) than the other models and a reasonable visual fit to the observed data, it does not have the statistical properties to sensibly project recurrences. This is a particular problem in the model the later the cure point is imposed or the lower the cure proportion is assumed to be. The company consider that if the EAG prefer the generalised gamma model for the DF->LR transition in the placebo arm on the grounds of lowest AIC, there is no reason not to adhere to TSD14 guidance and use this distribution for the DF->LR transition in the pembrolizumab arm as well. To do otherwise would be trading off an interpretable treatment effect on the DF->LR transition as well as clinical plausibility of the projected hazard function for a negligible 2 point advantage in AIC.

<u>The Gompertz curve is likely inappropriate</u>

Despite its superior statistical fit, the company excluded the Gompertz model from consideration for the placebo DF->DM transition because it has zero hazards very soon after the follow-up time. Given that we know ultra-late occurrences occur in early NSCLC, it is unclear why the placebo arm would be modelled to have zero DF->DM medium and long term recurrences, particularly when this is imposed on the placebo arm only and not the pembrolizumab arm, where patients continue to recur. While the combination of generalized-gamma/Gompertz has the best MSE of the 67 options for the placebo arm, we suggest the clinical implausibility of its projections means that the second best MSE option of generalized gamma/log-normal be considered superior. The statistical and visual fit are very similar and it adheres to TSD14 guidance in that using the log-normal model for the DF->DM transition matches the model that gives all the best fitting options by MSE in the pembrolizumab arm.

<u>OS Hazard Ratio in the EAG's model favours the placebo arm for most of the model's time horizon</u>

This can be seen by comparing the hazard of death from all causes using the graph provided in TP_AdjReg_1!AY:AY in the model. The company regards this as clinically implausible. Clinical expectation (and to the company's knowledge, the standard approach in oncology modelling in the early stage setting) is to consider an OS HR benefit for immunotherapy for a limited period, after which the hazards are broadly equalised between the arms rather than somehow becoming better in the control arm than the active treatment arm for the rest of the model.

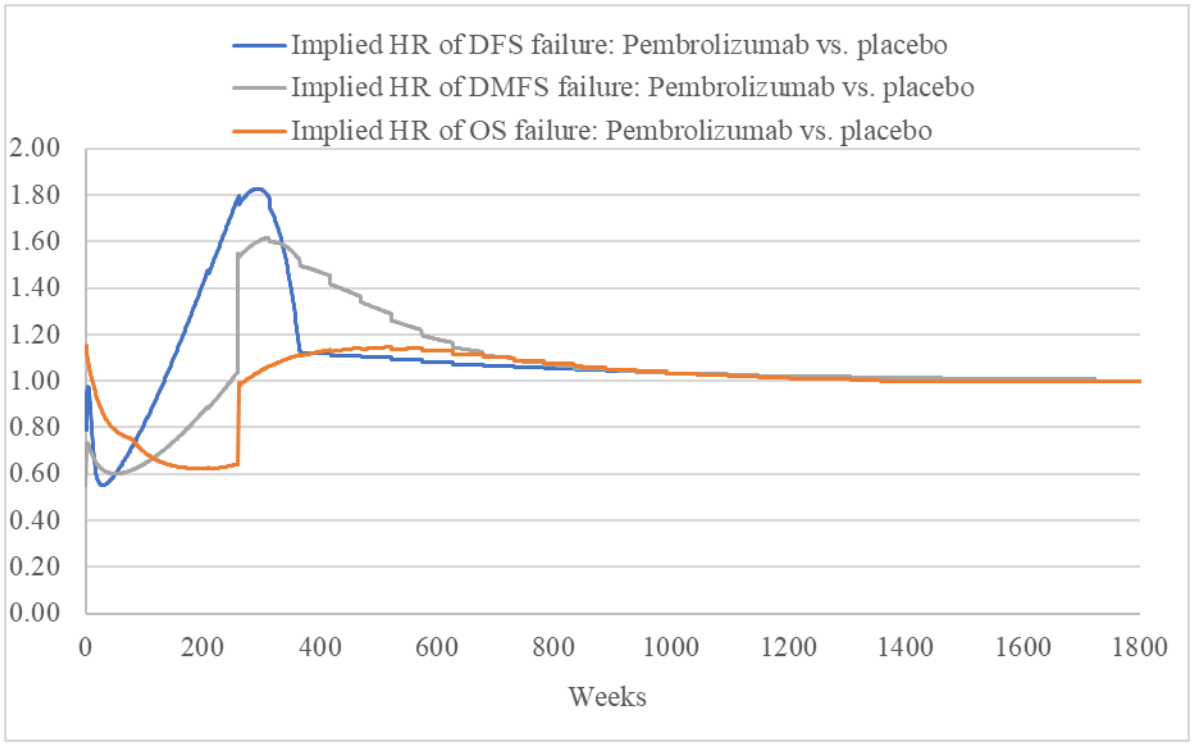


Figure 1: HRs of different outcomes in the model; EAG base case settings

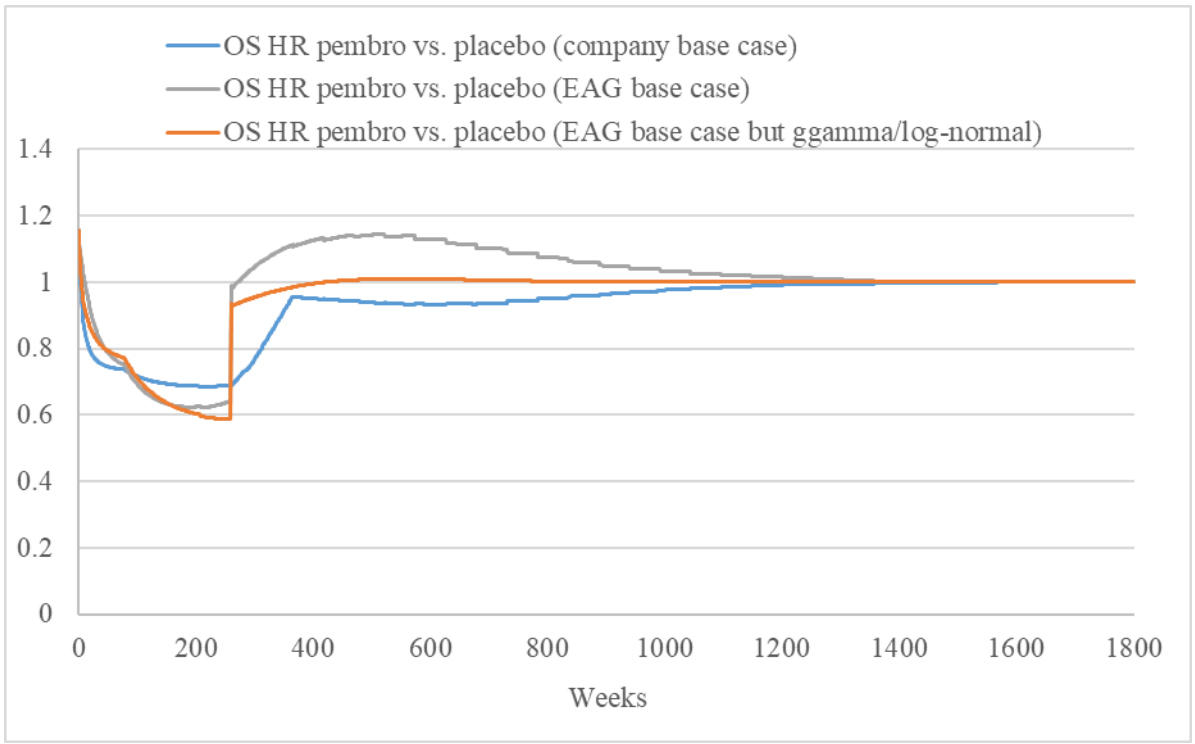


Figure 2: OS HR over time in model under different assumptions

The cure point is not known precisely and the model should be able to handle plausible variations

Below is an illustration of what happens in the EAG's model if the cure point is pushed back to 5-10 years (although this phenomenon occurs even if the cure point is pushed back to 5-8 years it is easier to see visually using 5-10 years). It is clinically implausible for DFS to be lower in the pembrolizumab arm.

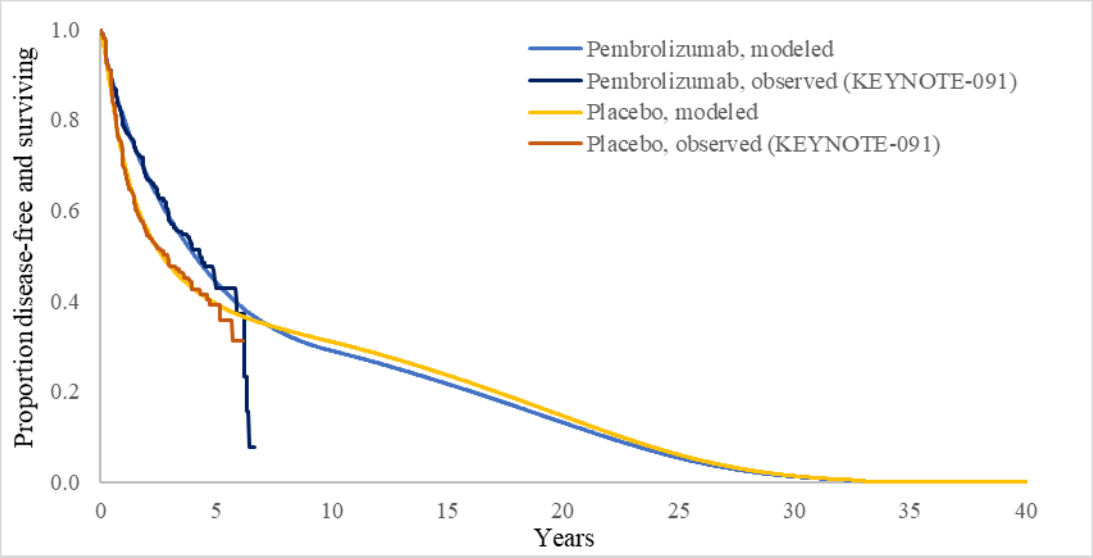


Figure 3: EAG Base case model but with 5-10 year gradual cure assumption

The EAG's model is not in line with the discussed literature on "ultra-late" recurrences

It is known that resected patients remain at risk of recurrences throughout their life and, although these recurrences are low after the typical period of active monitoring to 5 years, they should still be reflected in the economic model. We discussed this issue with the EAG in CQ B6 and illustrated that the company's base case model produced an "ultra-late" recurrence rate of 0.73%, which was similar to the 0.8% in the epidemiological study highlighted by the EAG. The EAG's model produces ultra-late recurrence rates of 0.15% in the placebo arm and 1.1% in the pembrolizumab arm. It is not clear to the company why it would be expected that the placebo arm had ultra-late recurrences more than five times lower than that observed in the study discussed with the EAG and why the pembrolizumab arm would have ultra-late recurrences 7.5 times higher than in the placebo arm.

These data can be seen by summing the DF->LR and DF->DM transitions that occur between 10.1 and 19.8 years in the model, as per the response to CQ B6.

The EAG's interpretation of evidence of treatment waning is not supported by the evidence

The EAG state more than 10 times in the EAR that there is evidence of treatment waning in KEYNOTE-091, which the company considers an very strong conclusion to draw based on the available evidence.

It is very important to note that in later years in KEYNOTE-091, routine follow up only occurs yearly and therefore the vast majority of patients are administratively censored by the later time points in the KM curves. The company notes that the absolute separation in the DFS curves at 1 year, 2 years,

3 years and 4 years is approximately 9%, 14%, 10% and 9%, meaning that there is a small increase in year 2 but otherwise the separation between the curves is relatively consistent at time points for which there are a reasonable amount of data. At the 4 year time point the KM-implied number of patients still DF is 178 in the pembrolizumab arm and 136 in the placebo arm whereas only 60 and 41 patients remain at risk respectively. This means that 2/3 of patients are censored, largely due to the long intervals between planned follow-up appointments in the trial. After 4 years there are a total of just 19 events in the trial. The company believes that to conclude there is evidence of treatment waning based on these data would be inappropriate as the numbers of events and patients at risk beyond 4 years are simply too small versus the administratively censored population.

<u>The use of differential distributions requires stronger evidence</u>

For the DF->LR transition the generalised gamma distribution has the lowest AIC by 10 points in the placebo arm and has a good visual fit. This appears to be the criteria by which the EAG selected it as appropriate. There is no meaningful difference in AIC (maximum 1-2 points) or visual fit for the DF->LR transition in the pembrolizumab arm. In the absence of other factors, this suggests that if following guidance in TSD14, the logical default pick for the pembrolizumab arm would also be the generalized gamma curve.

For the DF->DM transition, there are several potential reasons to select log-normal models for both arms.

- If ruling out the Gompertz model due to clinical implausibility in extrapolations (see above), the log-normal model has the best MSE when combined with the generalised gamma DF->LR transition in the placebo arm. (position 2 of the 49 non-proportional hazards models by MSE)
- Regardless of DF->LR transition, the log-normal model always has the best MSE in the pembrolizumab arm (positions 1-7 of the 49 non-proportional hazards models by MSE)
- Alternative picks by AIC would be Weibull, log-logistic and generalised gamma but these have poorer visual fit and MSE when combined with the preferred generalized gamma curves for DF->LR

<u>Pembrolizumab having zero treatment effect on cure is contrary to clinical expectation</u>

The EAG contend that pembrolizumab's only treatment effect is to delay recurrence and not improve the probability that a patient's radical treatment plan is genuinely curative. The company believes this is contrary to clinical expectation for several reasons:-

- At the 2023 advisory board, the company showed the advisors the Company base case extrapolated curves from the model which included a consistent separation of DFS curves consistent with improved cure rate on pembrolizumab. These extrapolations were confirmed as plausible.
- The advisors at the 2023 advisory board were clear that a cure point of 5 years, at which point DFS is always differential regardless of model, was reasonable. The advisors advised against implementing differential cure points by model arm, considering an analysis of this nature "arbitrary".
- Adjuvant treatment, even using standard chemotherapy, which is much less effective than pembrolizumab in NSCLC (at least in the metastatic setting, including in patients with PD-L1 <50%; see KN189, KN407 and resultant NICE technology appraisals) is offered to patients

with the expectation that it will improve the probability that the radical treatment plan is curative, not simply to delay recurrence.

Overall, the company considers the generalised-gamma/log-normal combination to be a reasonable alternative scenario to the base case

The generalised-gamma/log-normal model is a credible alternative to the company's base case for several reasons:-

- Good visual and statistical fit (2nd best model by MSE in the placebo arm and 7th best of 49 non-PH models in the pembrolizumab arm)
- Extrapolations do not result in implausible characteristics such as constant hazards, zero hazards, OS HR favouring placebo
- Adheres to TSD14 guidance to use the same distribution for transitions between the arms
- Alternative cure points may be examined without curves crossing
- No clinically unexpected early convergence of DFS curves
- Ultra late recurrences appear more reasonable at 0.4% in the placebo arm and 0.6% in the pembrolizumab arm
- OS HR complete convergence by 10 years suggesting no long term benefit for one arm or the other among non-cured patients, consistent with conservative approaches in other NICE appraisals of early stage oncology treatments

The company consider that the only limitation of the generalised-gamma/log-normal approach versus the company base case of log-normal/log-normal is that it underestimates observed OS to a greater degree. This is the reason why it was originally excluded from the final 7 in the company's curve selection algorithm (CS; Appendix N).

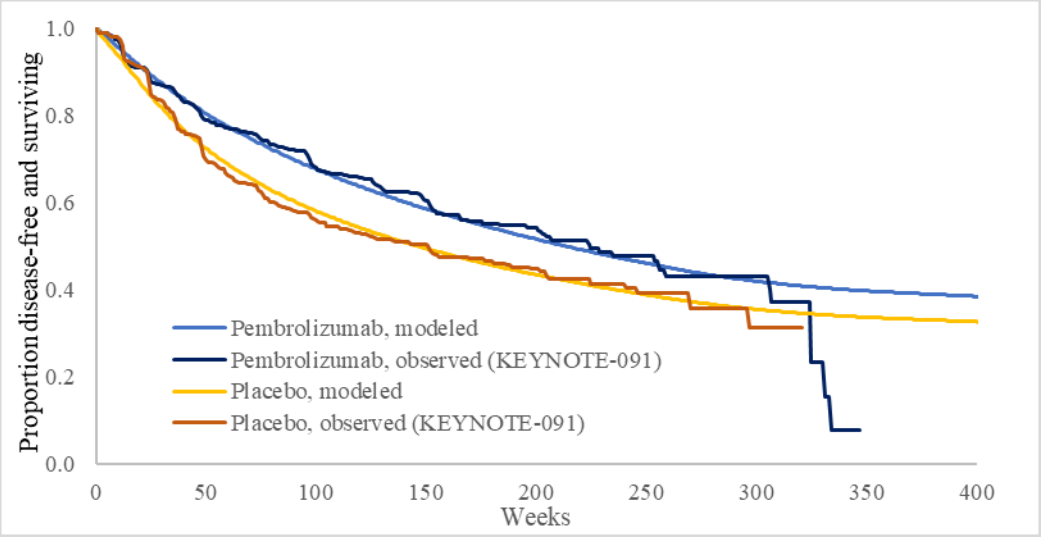


Figure 4: generalised-gamma/log-normal fit to observed DFS KM data

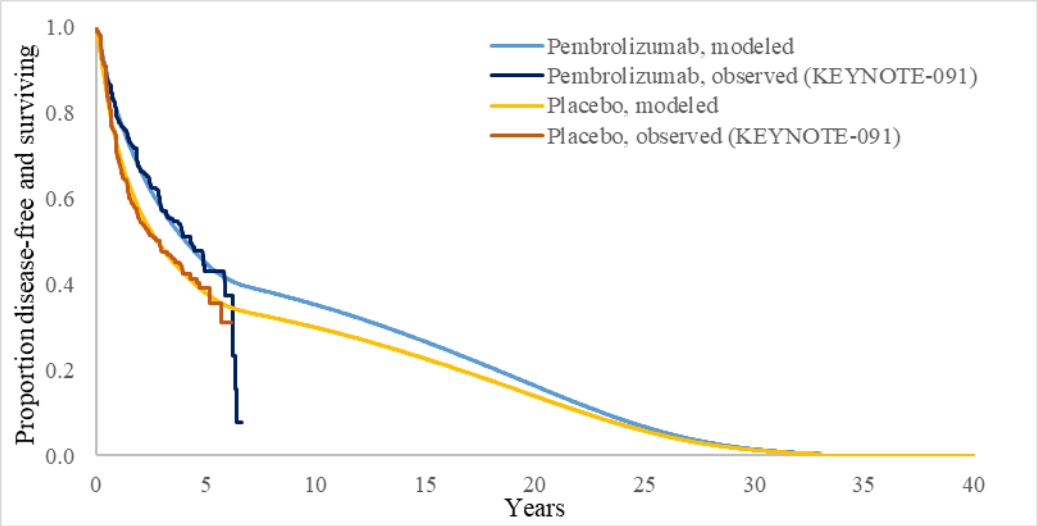


Figure 5: generalised-gamma/log-normal long term DFS projections

The company consider most other EAG changes to the model to be reasonable

We are providing this table in case it helps guide the NICE Technical Team and Committee Chair about which issues to spend time on during the meeting. It is our hope that minimal time would be devoted to discussing issues where the company do not wish to challenge the EAG's base case assumptions.

Table 1: EAG Base Case Assumptions and MSD Comments

Preferred assumption	Company View
PD-L1 <50% subpopulation baseline characteristics used	**Reasonable.**
Baseline age 68.4	**May be lower than this.**
Q6W dosing for 75% of pembrolizumab patients	**Reasonable.**
DFS for pemb = exp/log-normal	**Potentially unreasonable.**
DFS for placebo = gengam/gomp	**Potentially unreasonable.**
Calibration limited to 5 years	**Reasonable.**
I/O ineligible patients not calibrated	**Reasonable.**
Full KM for ToT	**Reasonable.**
Alternative 2nd line distant metastatic treatment costs	**Reasonable.**
PSSRU end of life cost	**Reasonable.**
DF utility include grade 1 and 2 AEs	**Reasonable.**

EAG scenario analyses using the generalised-gamma/log-normal curve selection along with other EAG preferred settings

Here we have attempted to replicate the EAG's preferred assumptions and were able to achieve an ICER that was very close; [redacted] in our model versus [redacted] in the EAG report. We have then updated the curve selection to the generalised-gamma/log-normal model and undertaken the EAG's "additional sensitivity analyses" where possible.

	Incremental costs (£)	Incremental QALYs	Incremental LYs	ICER vs. comparator (£/QALY)
Replicated EAG Base Case	[redacted]	0.49	0.61	[redacted]
G-gamm/log-normal+EAG base case	[redacted]	0.70	0.87	[redacted]
100%Q6W	[redacted]	0.70	0.87	[redacted]
Gen-gamma curves	[redacted]	0.70	0.87	[redacted]
Cure 7 Years	[redacted]	0.68	0.85	[redacted]
Differential cure points	Not implemented due to explicit advice at the advisory board against this			
Alternative LR transition (Imp010)	[redacted]	0.69	0.85	[redacted]
Equalise pembro and placebo after 7 years	Not implemented as unclear what this means			
Remove calibration	[redacted]	0.40	0.46	[redacted]

The company note that pembrolizumab is cost-effective under the majority of these scenarios. The only scenario in which the ICER is above NICE's conventional threshold is when the temporary calibration to OS is removed and the model no longer estimates the OS benefit that was observed within the trial. The company suggest this is uninformative as it is contrary to observed data.

Table 1 from the letter sent to NICE represents the list of the EAG's assumptions that MSD have agreed with (in green) which are applied in the updated base-case. In Table 2 MSD's updated base-case maintains the baseline age of 64.3 years and curve selections for DFS applied for both pembrolizumab and placebo (log-normal/log-normal) as per Document B. Table 3 includes a scenario where the updated base-case settings are applied with the exception of generalised-gamma/log-normal curve selections, which are applied to both treatments.

Table 1. List of assumptions in the EAG's model including modifications

Preferred assumption	Company View
PD-L1 <50% subpopulation baseline characteristics used	**Reasonable.**
Baseline age 68.4	**May be lower than this. MSD have set to 64.3 years**
Q6W dosing for 75% of pembrolizumab patients	**Reasonable.**
DFS for pemb = exp/log-normal	**Potentially unreasonable. MSD have set to log-normal/lognormal**
DFS for placebo = gengam/gomp	**Potentially unreasonable. Set to log-normal/lognormal**
Calibration limited to 5 years	**Reasonable.**
I/O ineligible patients not calibrated	**Reasonable.**
Full KM for ToT	**Reasonable.**
Alternative 2nd line distant metastatic treatment costs	**Reasonable.**
PSSRU end of life cost	**Reasonable.**
DF utility include grade 1 and 2 AEs	**Reasonable.**

Table 2. Updated-base case

Costs (£)	**Pembrolizumab**	**Placebo**	**Incremental (Pembrolizumab vs. Placebo)**
Costs, total and by category	[redacted]	[redacted]	[redacted]
Adjuvant treatment costs	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in LR state	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Radiotherapy costs	[redacted]	[redacted]	[redacted]

Salvage surgery costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in DM state	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Costs, total and by state	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Death (one-time terminal care costs)	[redacted]	[redacted]	[redacted]
<u>Effectiveness</u>			
Quality-adjusted life years (QALYs), total and by state	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
AE-related disutility	[redacted]	[redacted]	[redacted]
Age-related disutility	[redacted]	[redacted]	[redacted]
Life years (LYs), total and by state	**9.12**	**8.06**	**1.06**
Disease-free	7.11	5.90	1.21
Local-regional recurrence	0.71	0.56	0.15
Distant metastases	1.30	1.61	-0.30
Incremental outcomes (adjuvant			

pembrolizumab vs. comparator)			
Incremental costs (£)	-	-	[redacted]
Incremental QALYs	-	-	0.85
Incremental LYs	-	-	1.06
Incremental costs per QALY gained	-	-	[redacted]
Incremental costs per LY gained	-	-	[redacted]

Table 3. Scenario using alternative curve selection generalised-gamma/log-normal to both treatments

Costs (£)	**Pembrolizumab**	**Placebo**	**Incremental (Pembrolizumab vs. Placebo)**
Costs, total and by category	[redacted]	[redacted]	[redacted]
Adjuvant treatment costs	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in LR state	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Radiotherapy costs	[redacted]	[redacted]	[redacted]
Salvage surgery costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in DM state	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]

Costs, total and by state	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Death (one-time terminal care costs)	[redacted]	[redacted]	[redacted]
Effectiveness			
Quality-adjusted life years (QALYs), total and by state	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
AE-related disutility	[redacted]	[redacted]	[redacted]
Age-related disutility	[redacted]	[redacted]	[redacted]
Life years (LYs), total and by state	**9.15**	**8.24**	**0.91**
Disease-free	7.16	6.20	0.97
Local-regional recurrence	0.70	0.50	0.20
Distant metastases	1.29	1.54	-0.25
Incremental outcomes (adjuvant pembrolizumab vs. comparator)			
Incremental costs (£)	-	-	[redacted]
Incremental QALYs	-	-	0.73
Incremental LYs	-	-	0.91
Incremental costs per QALY gained	-	-	[redacted]
Incremental costs per LY gained	-	-	[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Response to company letter

July 2024

File name	Version	Contains confidential information	Date
		Yes	**05/07/2024**

Introduction

The EAG has reviewed the letter commenting on the selected DFS curves. The EAG appreciates receiving these critiques and notes prior to the committee meeting as it allows us time to address any major issues. However, because of the cure assumption, whichever extrapolation is chosen has relatively little impact in isolation. These curves are primarily an approximation of observed data, followed by a user manipulated reduction in rate of decline.

EAG response

The EAG responses to the company key issues are below:

a. **Company:** An exponential curve with constant hazard over time is conceptually unlikely to be appropriate for projecting recurrences in the adjuvant setting given both the EAG and company agree that there is a cured proportion (meaning hazards should decrease as the proportion of all disease-free patients who are cured will increase), particularly when it applies to only one arm.

EAG: Any theory on the reason why hazards appear constant is speculative, but this could plausibly be explained by treatment waning. As more patients recur there is a greater proportion of cured patients but, in the pembrolizumab arm only, there is also a number of patients who experience treatment waning. This is the best fitting curve to the observed data and following the period of observed data the cure assumption is applied.

b. **Company:** A Gompertz curve with zero hazard after the follow-up time is unlikely to be conceptually appropriate for modelling recurrences in the adjuvant setting, particularly when it applies to only one arm.

EAG: Thank you for identifying this issue. The EAG agrees that the long term recurrences are not appropriately accounted for in the EAG model due to the combination of the cure assumption and the gompertz curve. In the current EAG base case, approximately [redacted]% of patients experience an “ultra-late” recurrence

(between 10 and 20 years) as opposed to 12/1,458 (0.8%) recorded in Sonoda *et al.* 2019.

However, the EAG disagree that this is a problem caused by the choice of curve for modelling DF->DM. As noted at clarification and in the EAG report, the 95% cure rate was approximately derived in a previous NICE submission by attempting to match long term recurrence projected by the parametric curves to real-world data for HER2-positive early breast cancer. This means there is no objective clinical justification for this figure, 95% is an arbitrary reduction in the parametric curve used to match ultra-late recurrence rates to the curve that happened to be selected in that breast cancer submission. The percent reduction in recurrence risk in each arm would need to be reduced to approximately 75% for placebo patients in order to for ultra-late recurrence rates to approximately match Sonoda *et al.* 2019. Using this figure would lead to [redacted]% of patients in the placebo arm of the model to experience an ultra-late recurrence.

c. **Company:** The Overall Survival Hazard Ratio produced by the model under the EAG's curve selection is in favour of placebo from year 5 to year 26 in the model, after which point the HR=1. This is not clinically plausible.

EAG: This higher Overall Survival Hazard Ratio is driven by a higher rate of recurrences in the pembrolizumab arm from month 36 onwards. If recurrences occur at a higher rate between year 3 and 5 it seems plausible to expect a delayed higher hazard rate for OS in the pembrolizumab arm following year 5.

d. **Company:** The "cure point" in early NSCLC is not known precisely and, as discussed in the EAG report, a variety of assumptions have been examined in relevant NICE appraisals. If the committee are interested in sensitivity analyses where the cure takes place from 5-8 years instead of 5-7 years, for example, then DFS in the pembrolizumab arm is actually lower than the placebo arm, which would be clinically implausible.

EAG: The EAG agrees that it is likely implausible that the overall DFS or OS for pembrolizumab would ever decline below that of placebo and would accept a change to the model that limited pembrolizumab DFS from falling below the placebo. It is also worth noting in the EAG model that the percent reduction in recurrence risk in

each arm reached following the “cure point” is an arbitrarily defined reduction in the risk of two different curves. The EAG acknowledges there is significant uncertainty in the “cure point” but the cure rate is also significantly uncertain and dependent on the rate of decline predicted by the DFS curve and the expected “ultra long-term” recurrence rate. Given the nature of this value in the model there is no reason this should be expected to continue to provide plausible outcomes if changed in isolation given both values in combination are unknown.

e. **Company:** The EAG’s model produces “ultra-late” recurrences which are 0.18x the value discussed at Clarification Questions in the placebo arm, whereas “ultra-late” occurrences (>10 years) are 1.4x the value in the pembrolizumab arm. It is not clear why the “ultra-late” occurrence rate would be 7.5x higher in the pembrolizumab arm than in the placebo arm.

EAG: Please see response to company comment b.

f. **Company:** The use of differential distributions for the DF->LR and DF->DM transitions is contrary to guidance in TSD14. An option exists that adheres to the TSD14 guidance, while satisfying the EAG’s desire for very close visual fit to the KM data and not producing clinically implausibly projections; namely using generalized-gamma for both DF->LR transitions and log-normal for both DF->DM transitions.

EAG: Thank you for providing these updated curves. The EAG acknowledges that these provide a significantly better fit than the company base case. As stated in the report, the EAG believes there is sufficient evidence of treatment waning to justify using differential distributions, if this waning is accepted it would likely be an allowable exception to TSD14, if the committee reject this assumption the EAG accepts that gen-gamma/log-normal should be used. Results from this scenario on the EAG base case are shown in Table 1 below.

Table 1. Company’s base case results

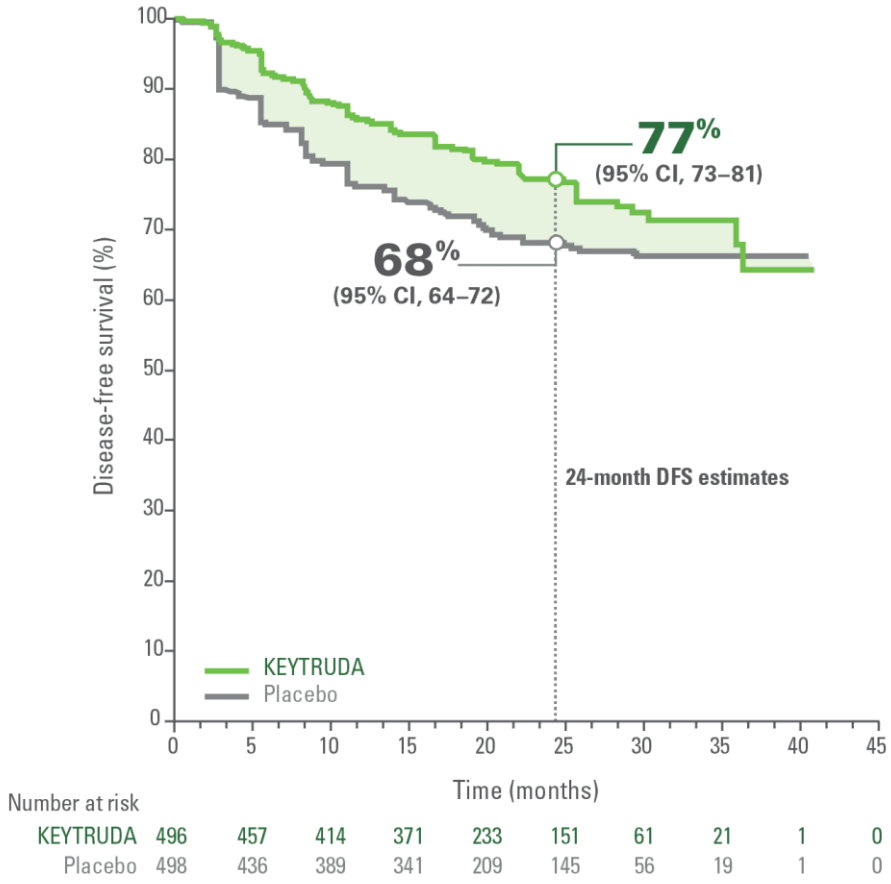
Intervention	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental Lys	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Pembrolizumab	[redacted]	8.58	[redacted]	-	-	-	-
Placebo	[redacted]	7.71	[redacted]	[redacted]	0.87	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year							

g. **Company:** The EAG is modelling pembrolizumab to have zero curative advantage; the only benefit being a delay in recurrences. This is contrary to advice received at the MSD 2023 UK advisory board where clinicians confirmed that the company's model including a differential proportion of cured patients was plausible.

EAG: As noted in the report, treatment waning was previously accepted in TA830 which assessed pembrolizumab for adjuvant treatment of renal cell carcinoma. The EAG does not disagree in principle about the clinical plausibility that pembrolizumab could lead to a higher proportion of cured patients; however, it does not appear to fit with the best fitting projections for DFS.

h. **Company:** The company considers that the EAG's interpretation that there is evidence of treatment waning in KEYNOTE-091 is not supported by the evidence. The gap between the curves only meaningfully narrows after 4 years, when approximately 2/3 of remaining DFS patients have been administratively censored (patients are only routinely followed up once per year at this point in the trial and therefore any asymptomatic recurrences will only be discovered at yearly follow-up). Very few events occur after 4 years (5 in the placebo arm and 14 in the pembrolizumab arm), compared to over 300 DFS patients, 2/3 of whom have been censored.

EAG: The EAG disagrees that a decrease in the DFS advantage going from 14% to 9% from year 2 to 4 is not a meaningful decrease. The EAG acknowledges there were more limited data available for year 5, but there is no alternative information to inform modelling. Furthermore, waning was previously accepted in TA830 which was informed by KEYNOTE 564. This trial appeared to have a similar limitation for data in the final year, as shown in the graph below, yet this did not prevent the committee from accepting treatment waning.



i. **Company:** Maintaining all the EAG's base case settings and selecting the generalised-gamma/log-normal curves in both arms results in an ICER of approximately [redacted]/QALY gained. The company consider this to be a much more reasonable conservative alternative to the base case than the approach presented in the EAG report.

EAG: Please see response to company comment f.

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Updated confidential appendix

July 2024

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135657.

1 Introduction

The External Assessment Group (EAG) produced this additional results document to provide the committee with the results of the updated economic model with prices/results that can be shared with the company. All analyses presented in this document include the patient access scheme (PAS) discount of [redacted] for pembrolizumab in the adjuvant and metastatic setting.

2 Company base case results

2.1 Company's base case results

Since submission of the EAG report the company have accepted a number of the EAG preferred assumptions as reasonable. The EAG preferred assumptions accepted/rejected by the company are shown in **Error! Reference source not found.**. In the case of the assumptions rejected, baseline age is assumed to come from the ITT population (64.3). The DFS curves are assumed to remain the same as the company base case (all log-normal).

Table 1: EAG Base Case Assumptions and MSD Comments

Preferred assumption	Company View
PD-L1 <50% subpopulation baseline characteristics used	Reasonable.
Baseline age 68.4	May be lower than this.
Q6W dosing for 75% of pembrolizumab patients	Reasonable.
DFS for pemb = exp/log-normal	Potentially unreasonable.
DFS for placebo = gengam/gomp	Potentially unreasonable.
Calibration limited to 5 years	Reasonable.
I/O ineligible patients not calibrated	Reasonable.
Full KM for ToT	Reasonable.
Alternative 2nd line distant metastatic treatment costs	Reasonable.
PSSRU end of life cost	Reasonable.
DF utility include grade 1 and 2 AEs	Reasonable.
Abbreviations: AE, adverse event; DFS, disease free survival; I/O, immunotherapy; KM, Kaplan-Meier; PD-L1, programmed death-ligand 1; Q6W, every 6 weeks; ToT, time on treatment.	

Table 2 presents the cost-effectiveness results of the company's updated (i.e., post EAG report) base case deterministic and probabilistic analyses. The probabilistic sensitivity analysis (PSA) conducted to assess the joint parameter uncertainty around base case results used a Monte Carlo simulation and derived probabilistic results from 1,000 generated simulations. When compared to the SoC, pembrolizumab produced a deterministic ICER of £[redacted] and probabilistic ICER of £[redacted].

Table 2. Company's base case results

Intervention	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Pembrolizumab	[redacted]	[redacted]	[redacted]	–	–	–	–
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results							
Pembrolizumab	[redacted]	[redacted]	[redacted]	–	–	–	–
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

The company's PSA scatterplot is presented in Figure 1 and cost effectiveness acceptability curve (CEAC) in Figure 2. Based on the analyses, the probability that pembrolizumab is cost-effective versus SoC at both a £20,000 and £30,000 willingness to pay (WTP) threshold is [redacted] and [redacted] respectively, using the company's base case assumptions.

Figure 1. Company's PSA scatterplot, reproduced from the company's model

Figure 2. Company's cost-effectiveness acceptability curve, reproduced from the company's model

2.2 Company's sensitivity analysis

The company conducted one-way sensitivity analyses (OWSA) to assess the sensitivity of the model to individual parameter uncertainty. The company produced a tornado diagram displaying the most influential parameters on the ICER, shown in Figure 3. This diagram is reproduced below based on the company's updated model.

Figure 3. One-way sensitivity analysis tornado plot, produced form the company's model

2.3 Company's scenario analysis

The company undertook a range of scenario analyses to explore the impact of alternative assumptions for key model parameters. Results of the company's scenario analysis were presented in the updated response to clarification and are reproduced by the EAG below.

Table 3. Scenario analysis conducted by the company

Scenario	Incremental costs (£)	Incremental QALYs	Incremental LYs	ICER
Base-Case	[redacted]	[redacted]	[redacted]	[redacted]
Cure point 5 years	[redacted]	[redacted]	[redacted]	[redacted]
Cure point 5-10 years	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab given Q6W	[redacted]	[redacted]	[redacted]	[redacted]
Exponential/log-normal DFS curves*	[redacted]	[redacted]	[redacted]	[redacted]
Weibull/log-normal DFS curves*	[redacted]	[redacted]	[redacted]	[redacted]

Log-logistic/log-normal DFS curves*	[redacted]	[redacted]	[redacted]	[redacted]
Gamma/log-normal DFS curves*	[redacted]	[redacted]	[redacted]	[redacted]
Approach #2 Gompertz/Weibull DFS curves*	[redacted]	[redacted]	[redacted]	[redacted]
Approach #3 Exponential/Exponential DFS Curves*	[redacted]	[redacted]	[redacted]	[redacted]
100% cure assumption	[redacted]	[redacted]	[redacted]	[redacted]

*The EAG notes that for this scenario the company reapplied the calibration

Abbreviations: AE, adverse event; DM, distant metastases; DFS, disease free survival; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LY, life-years; RDI, relative dose intensity; Q6W, every 6 weeks.

3 Additional economic analysis undertaken by the EAG

3.1 Exploratory and sensitivity analyses undertaken by the EAG

During the clarification stage, the External Assessment Group (EAG) requested a number of scenario analyses which were provided by the company.

Table 4. Results of the EAG's scenario analyses

	Results per patient	Pembrolizumab	Placebo	Incremental value
0	**Company base case post EAG report**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
Company scenarios in response to EAG clarification questions				
B2	Using baseline age from SEER†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B10	SMR 1.5†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B11	Using Impower010 in place of SEER for LR transitions (Nakamichi 2017, CRT and RT (TA823))†			

	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
B15	No re-treatment with pembrolizumab†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
EAG scenarios				
1	Baseline age changed to 68.4†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
3	DFS curves with improved fit; exponential/lognormal for LR/DM pembrolizumab patients and generalised-gamma/gompertz for LR/DM placebo patients†			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
4	Remove ramping (cure point 7 years)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
5	Differential cure point (7 years for pembrolizumab 5 years for placebo) †			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
Additional scenarios				
1	Company additional DFS scenario (Gen gamma DF->LR log normal DF->DM pembrolizumab and placebo) †			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]

†Recalibration was run on these model results

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year;

3.2 EAG preferred assumptions

In this section, the EAG presents its preferred analysis for the cost-effectiveness of adjuvant pembrolizumab for patients with resected non-small-cell lung cancer.

Table 5. EAG preferred model assumptions

Change number	Preferred assumption	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative ICER (£/QALY)
0	Company base case post EAG report	[redacted]	[redacted]	[redacted]
1	Baseline age 68.4	[redacted]	[redacted]	[redacted]
2	DFS for pemb = exp/log-normal DFS for placebo = gengam/gomp	[redacted]	[redacted]	[redacted]
Recalibration		[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; DFS, disease free survival; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; I/O, immunotherapy; KM, Kaplan Meir; QALY, quality-adjusted life-year; ToT, time on treatment.

3.2.1 EAG sensitivity analysis

The EAG's PSA scatterplot is presented in Figure 4 and cost effectiveness acceptability curve (CEAC) in **Error! Reference source not found.**. Based on the analyses, the probability that pembrolizumab is cost-effective versus placebo at both a £20,000 and £30,000 willingness to pay (WTP) threshold is [redacted] and [redacted], respectively, using the EAG's base case assumptions.

Figure 4. EAG's base case PSA scatterplot

Figure 5. EAG's base case cost-effectiveness acceptability curve

The EAG conducted one-way sensitivity analyses (OWSA) to assess the sensitivity of the model to individual parameter uncertainty. The EAG tornado diagram displaying the most influential parameters on the ICER is displayed below based on the EAG's updated model.

Figure 6. OWSA tornado plot. Produced from EAG's base case model

Abbreviations: DF, disease-free; DM, distant metastatic recurrence; local recurrence; ICER, incremental cost-effectiveness ratio; PFS, progression-free-survival; NSCLC, Non-Small Cell Lung Cancer; OS, overall survival; OWSA, one-way-sensitivity-analysis; QALY, quality adjusted life years.

3.3 EAG additional sensitivity analyses

The following additional sensitivity analyses were also undertaken using the EAG's preferred analysis:

Table 6. EAG additional sensitivity analyses, applied to the EAG preferred base case analysis

	Results per patient	Pembrolizumab	Placebo	Incremental value
0	**EAG preferred analysis**			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
1	100% Q6W			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]

2	Gen gamma DF to LR pembrolizumab*			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
3	Cure 7 years (no ramping)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
4	Differential cure point 5 years for placebo 7 for pembrolizumab			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
5	Alternatives to SEER LR transition (recalibration)*			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
6	Equalise pembrolizumab and placebo after 7 years			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
7	Remove calibration			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
8	Company additional DFS scenario (Gen gamma DF->LR log normal DF->DM pembrolizumab and placebo)*			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
9	Differential percent reduction in risk (75% for placebo, 95% for pembrolizumab)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]

*The EAG notes that for this scenario the company reapplied the calibration

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year;

LYG (years)	Pembrolizumab	Placebo	Incremental
Starting age: 64.3 years			
Company DFS curves (base case)	9.11	8.01	1.10
Company alternative DFS curves	9.15	8.21	0.94
EAG DFS curves	9.03	8.42	0.61
Starting age: 68.4 years			
Company DFS curves	8.55	7.57	0.98
Company alternative DFS curves	8.58	7.71	0.87
EAG DFS curves (base case)	8.5	7.88	0.62