Single Technology Appraisal

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID5094]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID5094]

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**

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

5. **External Assessment Report prepared by Liverpool Reviews and Implementation Group**

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

7. **Expert personal perspectives:**
   a. Toby Talbot, Consultant Clinical Oncologist at the Royal Cornwall Hospital NHS Trust – clinical expert, nominated by Merck Sharpe & Dohme (company)

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID5094]

Document B

Company evidence submission

March 2024

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Abbreviations

Abbreviation/acronym	Definition
1L	First line
2L	Second line
AE	Adverse event
AEOSI	Adverse event of special interest
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
APaT	All Participants as Treated
AUC	Area under the curve
BICR	Blinded independent central review
BIPR	Blinded independent pathologic review
BNF	British National Formulary
BSC	Best supportive care
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CPI	Consumer price index
CrI	Credible interval
CRT	Chemoradiotherapy
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DIC	Deviance Information Criterion
DM	Distant metastases
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
EF	Event free
EFS	Event free survival
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EMR	Electronic medical record
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQoL-5D
EU	European Union
FA	Final Analysis
FAD	Final appraisal determination
FAS	Full Analysis Set
GP	General practitioner

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HCC	Half cycle correction
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health related quality of life
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
IO	Immunotherapy
ITT	Intention to Treat
IV	Intravenous
KM	Kaplan-Meier
KOL	Key opinion leader
LR/P	Locoregional recurrence or progression
LY	Life years
LYG	Life year gained
MAA	Marketing authorisation application
MHRA	Medicines and Healthcare products Regulatory Agency
mPR	Major pathological response
MRI	Magnetic resonance imaging
MSE	Mean squared error
N/A	Not applicable
N/R	Not reported
NAC	Neoadjuvant chemotherapy
NCI	National Cancer Institute
NDRS	National Cancer Registration and Analysis Service
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLCA	National Lung Cancer Audit
NMA	Network meta-analysis
NSCLC	Non small lung cancer
ONS	Office for National Statistics
ORR	Objective response rate
OS	Overall survival
pCR	Pathological complete response
PDC	Platinum doublet chemotherapy
PD-L1	Programmed death-ligand 1
PD-L1/2	Programmed death-ligand 1/2
PET	Positron emission tomography
PET-CT	Positron emission tomography–computed tomography
PFS	Progression-free survival
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit

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QALY	Quality-adjusted life year
QLQ-C30	Core quality of Life questionnaire
QxW	Every x weeks
RCT	Randomised controlled trial
RT	Radiotherapy
SABR	Stereotactic ablative radiotherapy
SCLC	Small cell lung cancer
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TEW	Treatment effect waning
TKI	Tyrosine kinase inhibitor
TNM	Tumour Node Metastasis
ToT	Time on treatment
TPS	Tumor Proportion Score
TSD	Technical Support Document
UICC	Union for International Cancer Control
UK	United Kingdom
WHO	World Health Organisation

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

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

Decision problem

- Pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, then continued as a monotherapy as adjuvant treatment, is proposed as an option for the management of adults with resectable non-small cell lung cancer (NSCLC) that is at high risk of recurrence.
- The indication specified in the decision problem is in line with the anticipated marketing authorisation for pembrolizumab in resectable NSCLC.
- MSD's submission predominantly aligns with the final scope issued by NICE, with the exception of.
    - Event-free survival (EFS) was a co-primary outcome in the pivotal trial evaluating pembrolizumab as a peri-adjuvant treatment (KEYNOTE-671) and, therefore, data on disease-free survival are not available.
    - MSD do not consider chemoradiotherapy to be a relevant comparator for pembrolizumab in the setting that is the focus of this Technology Appraisal.

Technology

- Pembrolizumab (KEYTRUDA®) is a humanised monoclonal antibody (mAb) against the programmed death-1 (PD-1) receptor.
- Expression of PD-1 protein, and its ligands PD-L1 and PD-L2, triggers a signalling cascade that culminates in the suppression of T cell proliferation, cytokine release and cytotoxicity, a process that modulates the immune response (to prevent destruction of healthy cells).

Health condition

- In the UK, lung cancer is the third most common cancer, and is by far the leading cause of cancer deaths, accounting for around a fifth (21%) of all cancer deaths in females and males combined.
- In its early stages, lung cancer can be asymptomatic. Many cases of lung cancer are diagnosed when the disease has reached a more advanced stage (about 50% are locally advanced or metastatic), with some diagnoses arising incidentally from investigations for other conditions.
- Histology and tumour stage are key prognostic factors, and determine the management of the condition.

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- Although prognosis is more favourable if NSCLC is diagnosed at an early stage, the risk of recurrence is high, and disease typically recurs at a more advanced, often metastatic, stage.

Clinical care pathway

- NICE guidance recommends various treatment options for early stage NSCLC, depending on stage of disease and patient preference, with the mainstay of treatment being surgery.
- Available treatment options include neoadjuvant nivolumab plus platinum-based chemotherapy, and chemotherapy and radiotherapy, or a combination of the two.
- Pembrolizumab in combination with platinum-based chemotherapy followed by adjuvant pembrolizumab monotherapy is anticipated to be used as an option for adults aged 18 or over with resectable stage II, IIIA, or IIIB (T3/4N2) NSCLC (AJCC/UICC version 8).
- No equity or equality considerations are anticipated.

B.1.1. Decision problem

The submission covers the technology's full anticipated marketing authorisation for this indication, which is expected to allow use of pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, then continued as a monotherapy as adjuvant treatment, for the treatment of adults with resectable non-small cell lung cancer (NSCLC) that is at high risk of recurrence (Table 2).(1) The company submission (CS) deviates from the final scope(2) issued by the National Institute for Health and Care Excellence (NICE) in some of the comparators considered relevant to the appraisal, as detailed in Table 1.

The decision problem addressed in this submission is presented in Table 1.

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Table 1. The decision problem(2)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated resectable non-small-cell lung cancer	As per final scope	N/A
Intervention	Pembrolizumab with chemotherapy for neoadjuvant treatment then pembrolizumab monotherapy as adjuvant treatment	As per final scope	N/A
Comparator(s)	Established clinical management without pembrolizumab, which may include: • Neoadjuvant nivolumab with chemotherapy • Neoadjuvant chemoradiotherapy • Platinum based chemotherapy • Active monitoring • Durvalumab (subject to NICE appraisal) • Osimertinib (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)	Comparators addressed in submission: • Neoadjuvant nivolumab with chemotherapy; • Platinum-based chemotherapy • Active monitoring (i.e., surgery alone).	After reviewing NICE guideline 122 (NG122)(3) and consulting with clinical experts, MSD do not consider neoadjuvant chemoradiotherapy to be a relevant comparator for peri-adjuvant pembrolizumab, and do not present effect estimates for the comparison. MSD note that the recommendation in NG122 for use of neoadjuvant chemoradiotherapy plus surgery has only a weak "consider" type recommendation and the guidance is restricted to patients who are stage IIIA-N2 and only those who are considered fit enough for surgery. Subgroup analyses for the specific population were not carried out because: • data were not reported separately in the comparator trials of interest for stage IIIA-N2 patients, therefore subgroup analysis was not feasible; • clinical experts consulted by the company confirmed that this regimen was either not in use or

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			had been supplanted by neoadjuvant nivolumab plus chemotherapy. The treatments listed below are not considered relevant comparators as they are either under assessment by NICE or only available through the Cancer Drugs Fund, and are therefore not considered standard of care: • durvalumab;(4) • osimertinib;(5) • atezolizumab.(6)
Outcomes	The outcome measures to be considered include: • disease-free survival; • event-free survival; • pathological complete response; • overall survival; • response rates; • adverse effects of treatment; • health-related quality of life.	As per final scope, with the exception that response rates and disease-free survival are not reported.	MSD note that response rates were not collected in the KEYNOTE-671 study. MSD suggest that response rate might not be a clinically relevant outcome in the early stage setting for lung cancer where systemic treatments are given to preclude development and growth of micro-metastases, with surgery the mainstay of the treatment plan. The pivotal trial informing this submission (KEYNOTE-671) assessed EFS, rather than DFS, as a co-primary outcome, which was defined as the time from randomisation to the first of: disease or local progression; inability to resect tumour; local or distant recurrence; or death. As noted in TA876,(7) in the neoadjuvant and peri-adjuvant setting, EFS is an appropriate outcome as it also captures events that preclude surgery.

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Subgroups to be considered	If the evidence allows subgroups will be considered based on: • Whether pembrolizumab is used before and after surgery • PD-L1 tumour proportion score • Disease stage • Presence of biological or genetic markers	Of the subgroups listed, disease stage at baseline and PD-L1 tumour proportion score were both stratification factors at randomisation in KEYNOTE-671 and are pre-specified subgroup analysis within the study protocol. Results for EFS by PD-L1 status are presented for TPS<1%, TPS ≥1%, TPS 1–49%, and TPS ≥50%. EFS is reported separately for stage II and stage III NSCLC. Data are not available for presence of biological or genetic markers (other than PD-L1 TPS) and whether pembrolizumab is used before and after surgery.	Presence of biological or genetic markers (other than PD-L1 status) was not routinely captured at patient enrolment in KEYNOTE-671. At the time of writing, presence of genetic markers, such as EGFR mutations and ALK translocations, is not routinely assessed at the point of neoadjuvant (and therefore peri-adjuvant) treatment for NSCLC in UK clinical practice. However, given the availability of treatments targeting EGFR and ALK abnormalities, testing is likely to become more common. Genetic markers are more commonly used to direct treatment for patients receiving adjuvant therapy, or for those with metastatic disease. Data on extent of use of pembrolizumab before and after surgery are reported in the submission. However, estimates of comparative clinical effectiveness by whether pembrolizumab was or was not used after surgery are not reported. The trial protocol for KEYNOTE-671 mandated that everyone who underwent surgery be given adjuvant treatment, irrespective of any patient characteristic. The cost effectiveness of actively selecting not to use pembrolizumab after surgery is explored in scenario analyses whereby it is assumed that patients who achieve a pCR after neoadjuvant therapy receive no further treatment after surgery. MSD note that KEYNOTE-671 was not powered to detect a difference in clinical effectiveness between the treatment

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			groups in any subgroup. Thus, the results of subgroup analyses will be hypothesis generating and should be interpreted with caution.

Abbreviations: AJCC, American Joint Committee on Cancer; ALK, Anaplastic lymphoma kinase; DFS, Disease-free survival; EFS, Event-free survival; EGFR, Epidermal growth factor receptor; NSCLC, Non-small cell lung cancer; pCR, Pathological complete response; PD-L1, Programmed death-ligand 1; TPS, Tumour proportion score.

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B.1.2. Description of the technology being evaluated

Pembrolizumab (KEYTRUDA®) is a humanised monoclonal antibody (mAb) against the programmed death-1 (PD-1) receptor. Expression of PD-1 protein, and its ligands PD-L1 and PD-L2, triggers a signalling cascade that culminates in the suppression of T cell proliferation, cytokine release and cytotoxicity, a process that modulates the immune response (to prevent destruction of healthy cells).(8) Expression of PD-L1 and PD-L2 is frequently upregulated on the surface of tumour cells, as well as other cells in the tumour microenvironment. By binding to the PD-1 receptor, and thus blocking its interaction with PD-L1 and PD-L2, pembrolizumab reverses PD-1-mediated T-cell suppression, thereby reactivating tumour-specific cytotoxic T lymphocytes and restoring antitumour immunity.

A description of pembrolizumab and its proposed use for the treatment of early stage non-small cell lung cancer (NSCLC) is available in Table 2. The draft Summary of Product Characteristics (SmPC) is provided in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Pembrolizumab (KEYTRUDA)
Mechanism of action	Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor, thereby potentiating an immune response to tumour cells.
Marketing authorisation/CE mark status	An application for marketing authorisation (MA) was submitted to the European Medicines Agency (EMA) in March 2023. The Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on 22 February 2024 recommending approval of pembrolizumab for use in the indication listed in the application.(1) The anticipated date of EMA Marketing Authorisation (MA) is [redacted]. An application for a MA for Great Britain was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) in March 2024, using the EMA as the reference regulatory body. The anticipated date of approval by the MHRA is [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication wording, based on the positive opinion from the CHMP, is: Pembrolizumab (KEYTRUDA ®) in combination with platinum-containing chemotherapy as neoadjuvant treatment, then continued as a monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung cancer (NSCLC) at high risk of recurrence in adults. Pembrolizumab has also obtained regulatory approval for the management of the following conditions: • Melanoma;

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	• NSCLC • Classical Hodgkin lymphoma; • Urothelial carcinoma; • Head and neck squamous cell carcinoma • Renal cell carcinoma; • Microsatellite instability high or mismatch repair deficient cancers; • Colorectal cancer; • Oesophageal carcinoma; • Triple-negative breast cancer; • Endometrial carcinoma; • Cervical cancer; • Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma; • Biliary tract carcinoma.
Method of administration and dosage	The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.
Additional tests or investigations	For subgroup analysis in which a stopping rule is applied to pembrolizumab for those patients achieving a pathological complete response, additional pathology is required post-surgery as assessing pathological response is not currently routine practice.
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) for pembrolizumab is in place. Please refer to Appendix K for details of discount.

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

B.1.3.1. Health condition

Lung cancer originates in the cells of the respiratory system, predominantly the epithelial cells, and can affect the trachea (windpipe), bronchi (airways) and alveoli (air sacs).(9) In 2020, about 2.2 million people globally received a diagnosis of lung cancer, which accounts for 11.4% of all new cancer diagnoses and makes lung cancer one of the most common types of cancer. Additionally, lung cancer is a leading cause of cancer deaths worldwide, with about 1.8 million deaths (18.0% of cancer deaths) attributed to lung cancer in 2020.(10)

There two main types of lung cancer, which are differentiated based on histology: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).(11) NSCLC is the more common form of the two, accounting for approximately 80%–85% of all lung cancers, whereas SCLC is the more aggressive disease.(9)

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NSCLC can be characterised further based on histology into two principal subtypes — squamous cell carcinoma (25%–30%) and non-squamous NSCLC (75%).(11) Squamous cell carcinoma develops in the squamous cells, which are flat cells lining the surface of the airways in the lungs, and typically originates close to the centre of a bronchus.(12) Non-squamous NSCLC, which usually manifests in peripheral lung tissues, encompasses adenocarcinoma (~40%) and large cell carcinoma (~5%–10%), and other less frequently occurring subtypes such as adenosquamous carcinoma and sarcomatoid carcinoma.(9) The individual subtypes classified as non-squamous NSCLC each originate from different types of lung cell but are grouped together because their treatment and prognoses are frequently similar.

Smoking tobacco is the largest risk factor for developing lung cancer.(13) Around 90% of people who are diagnosed with lung cancer are smokers or ex-smokers, and starting smoking at a younger age further increases the risk. In the UK, 72% of lung cancer cases have been attributed to smoking. Breathing in the smoke of others, also referred to as second-hand smoking, increases the risk of non-smokers for developing lung cancer. Older age is a risk factor, with about 40% of people diagnosed with lung cancer being aged 75 and over. Other risk factors include exposure to causative agents such as radon, air pollution, asbestos and heavy metals.

As with many cancers, in its early stages, lung cancer can be asymptomatic.(9) Many cases of lung cancer are diagnosed when the disease has reached a more advanced stage (about 50% are locally advanced or metastatic),(11) with some diagnoses arising incidentally from investigations for other conditions. Additionally, many of the signs and symptoms of lung cancer can also be caused by other medical conditions, which can make diagnosis challenging, particularly if a person also has a co-existing respiratory condition such as chronic obstructive pulmonary disease. As lung cancer progresses, the most common symptoms that people experience are a persistent new cough, breathlessness, chest and shoulder pain, fatigue, unexplained weight loss and loss of appetite.

B.1.3.1.1. Diagnosis and staging

The first investigation people with suspected lung cancer usually undergo is a chest X-ray.(3, 14) Should the X-ray suggest the presence of an abnormality, patients are then referred for a contrast-enhanced chest computerised tomography (CT) scan to confirm the diagnosis and determine the stage of the disease: chest X-rays do not provide images of sufficient detail for a definitive diagnosis of lung cancer. Biopsy or further imaging (e.g., magnetic resonance imaging [MRI] or positron emission tomography-CT) may be needed for staging of disease

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and to detect specific markers that can guide treatment strategy, particularly for those who could be candidates for treatment with curative intent.

Stage of NSCLC is determined using the Tumour–Node–Metastasis (TNM) system of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC),(15) which utilises three features of a tumour (Table 3):

- Size and extent of the primary tumour (T);
- Location of involved lymph nodes (N);
- Presence of distant metastases (M).

More details about the characteristics of a tumour are provided through the addition of numbers and/or letters to each of the individual components of the TNM classification. Numbers denote how advanced the cancer is, the higher the number the more advanced the cancer. Letters provide more granularity on the parameter, for example, tumour size and to which part of the body the cancer has spread. For example, using the 8th edition of the AJCC/UICC, stage IB describes a tumour that is, at its largest dimension, larger than 3 cm but smaller than 4 cm and that has not invaded the lymph nodes or spread outside the lung (Table 3).

Typically, stages I and II denote early stage lung cancer, whereas stage III corresponds to locally advanced disease. Patients diagnosed with stage I to III lung cancer have a better prognosis than those receiving a new diagnosis of stage IV (metastatic) disease.(16) Treatment options available to those with stage I to III lung cancer, predominantly surgery and chemotherapy, are often given with curative intent. However, a proportion of people (30%–55%) experience recurrence of their disease after surgery, with recurrence most commonly occurring at distant, that is metastatic, sites.(17)

The eighth edition of the AJCC/UICC was published in 2017.(18) For staging of lung cancer, notable changes from the seventh edition are the creation of a new stage, stage IIIC, and revision of the classifications of size of tumour, resulting in many subclassifications of stage encompassing smaller tumours when compared with the seventh edition (Table 3).(19) The pivotal trial from which the evidence on clinical effectiveness of pembrolizumab when used neoadjuvantly followed by adjuvantly (i.e., peri-operative/peri-adjuvant setting) is derived — KEYNOTE-671(20) — used the 8th edition of the AJCC/UICC for staging of lung cancer. Various staging systems are used across the clinical studies that inform the estimate of comparative clinical effectiveness for pembrolizumab in the peri-adjuvant setting, due to the time period over which the studies were carried out. The potential impact of disparity in

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staging systems on interpretation of the results generated by the network meta-analysis (NMA) is described and discussed (please see Section B.2.8).

Table 3. Overview of the changes in staging from the 7th to the 8th edition of the AJCC/UICC system(19)

Stage	TNM categorisation	
	Seventh edition[a,b]	Eighth edition[a,b]
IA	N0, M0, T1a/b (≤3 cm)	N0, M0, T1a/b/c (≤3 cm)
IB	N0, M0, T2a **(>3–5 cm)**	N0, M0, T2a **(>3–4 cm)**
IIA	N0, M0, T2b **(>5–7 cm)** N1, M0, T1/T2a (≤5 cm)	N0, M0, T2b **(>4–5 cm)**
IIB	N0, M0, T3 **(>7 cm)** N1, M0, T2b (5–7 cm)	N0, M0, T3 **(>5–7 cm)** N1, M0, T1/T2 (≤5 cm)
IIIA	N0, M0, T4 N1, M0, T3/4 (>7 cm or invasive) N2, M0, T1–3 (any size, non-invasive)	N0, M0, T4 **(>7 cm)** N1, M0, T3/4 **(>5 cm)** N2, M0, T1/2 (≤5 cm)
IIIB	N2, M0, T4 N3, M0, Any T (any size)	N2, M0, T3/T4 **(>5 cm)** N3, M0, T1/T2 **(≤5 cm)**
IIIC	Not included	N3, M0, T3/T4 (>5 cm)
IV	Any N, M1a/b, Any T	Any N, M1a/b, Any T Any N, M1c, Any T

[a] Text in bold identifies the fields that have changed in the revision of the 7th to the 8th edition of the AJCC/UICC system.

[b] The numbers allocated to T range from 1 to 4, with increase in tumour size with increasing number. The numbers allocated to N range from 0 to 3, where 0 indicates no lymph node involvement and 3 denotes that numerous lymph nodes are affected. M is attributed either 0 or 1, where 0 means no metastasis and 1 indicates that distant metastases have been identified.(9)

Abbreviations: AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control.

In addition to stage of disease and histologic subtype, presence of molecular markers (i.e., a mutation in a gene sequence) is also a key prognostic factor in NSCLC, and there are treatment options that target specific markers. Biomarker testing is carried out to determine the optimal treatment for patients with newly diagnosed NSCLC. In addition to PD-L1, other commonly observed biomarkers in NSCLC for which there are NICE recommended treatment options, include epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK).(5, 21-23) Therapeutics targeting EGFR and ALK biomarkers have been shown to improve overall survival (OS), typically in locally advanced or metastatic disease, for those carrying the marker, but most people with NSCLC are EGFR and ALK negative:(24) globally, about a third of patients carry the EGFR sensitising mutation(25) and only 5–7% harbour the ALK mutation.(26) In the UK, about 10%–15% of people with NSCLC have been found to harbour EGFR mutations.(11) It is noted that those with resectable

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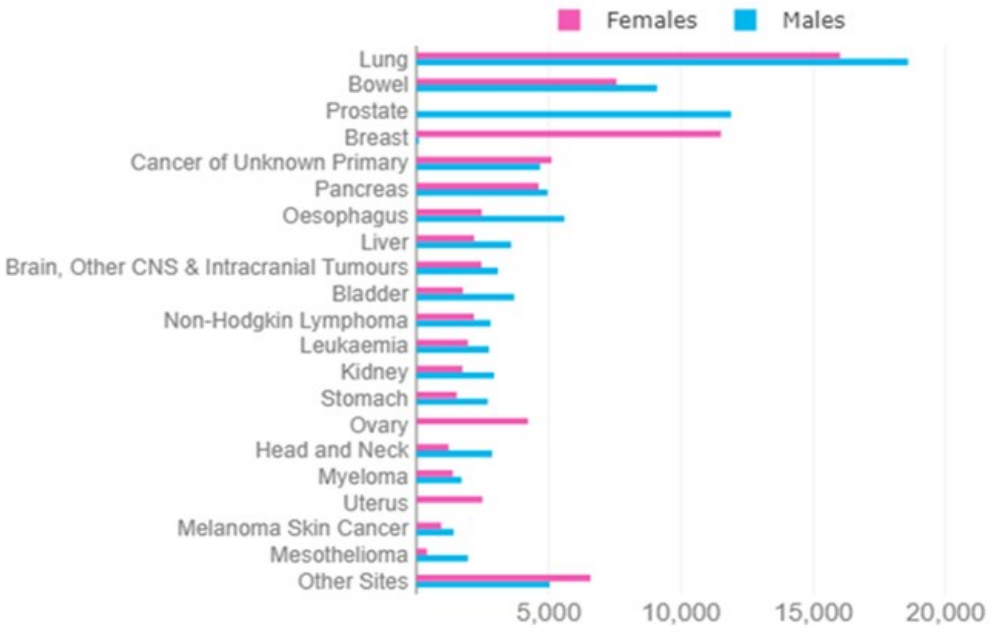
disease and who carry a biomarker are not typically considered for treatment with an immunotherapy, such as pembrolizumab.(3)

B.1.3.1.2. Epidemiology

As noted above, lung cancer is one of the most commonly occurring cancers worldwide. In the UK, lung cancer is the third most common cancer, and is by far the leading cause of cancer deaths, accounting for around a fifth (21%) of all cancer deaths in females and males combined (Figure 1).(16) For the period 2017 to 2019, about 34,800 deaths in the UK were attributed to lung cancer each year, which averages out to 95 deaths each day.(16) Mortality is highest in people aged 85 to 89. Lung cancer incidence rates have remained stable over the past decade in the UK and are projected to fall by 2% by 2040.

Lung cancer affects men and women equally in the UK, with the division between females and males being 48% and 52%. However, although overall incidence rates have remained stable for the past decade, rates in females have increased by around 13%, whereas rates in males have decreased by 12% (2016–2018). Incidence and mortality from lung cancer have been shown to be strongly linked to socioeconomic status and deprivation, with mortality rates in England being 170% higher for males and 176% higher for females who live in the most deprived compared with the least deprived areas of the country.(16)

Figure 1. The 20 most common causes of cancer deaths in the UK (2017–2019)(16)



According to NHS Digital, in 2021, 39,635 patients were diagnosed with lung cancer in England.(27) By contrast, the National Lung Cancer Audit (NLCA), which uses a different

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source to NHS Digital, reported 34,478 diagnoses of lung cancer in England for the same time period, with average age at diagnosis of 74 years.(11) Over 90% of cases were determined to be NSCLC. The NLCA also reported that the number of patients diagnosed in England in 2021 had returned to levels reported before the COVID-19 pandemic.

At the time of writing, a large proportion of lung cancers are diagnosed when the cancer has reached an advanced stage, that is, either locally advanced (stage III), in which the lymph nodes are involved and the cancer has spread to other parts of the lung, or metastatic (stage IV), where the cancer has reached organs in other parts of the body (Table 5). Of the 34,478 new diagnoses of lung cancer reported by the NLCA, nearly 50% were classified as stage IV at presentation.(11) Additionally, about 40% of patients were diagnosed with stage I–III lung cancer, making them candidates for what could be curative surgery (Table 4).(11) As stage III lung cancer covers many different types of tumour, which may or may not involve lymph nodes, and which might have spread to sites near to the lung, not all stage III cancers are resectable. In KEYNOTE-671,(20) eligibility criteria for enrolment into the study limited stage III NSCLC to IIIA and IIIB based on the 8th edition of the AJCC/UICC (Table 3).(18)

Table 4. Stage of lung cancer at diagnosis(11)

Stage at diagnosis (2021)	Percentage of all cancers diagnosed
I	19.6
II	6.8
IIIA	10.6
IIIB/C	8.0
IV	41.0
Unknown	14.0

Despite advances in diagnosis and the introduction of innovative treatments to the pathway, 5-year survival for lung cancer remains poor (26.3%), particularly for those with metastatic disease, with only 8 out of 100 metastatic patients being alive at 5 years after their diagnosis (Table 5).(28) Those identified as having early stage lung cancer have a better prognosis compared with those with metastatic disease, with 5-year survival for stage I patients being 67.8% (Table 5). As would be expected, the later the stage of lung cancer, the worse the prognosis, but, even for stage III cancer, 5-year survival is about only 25%. In a bid to detect and treat lung cancer earlier, NHS England is introducing a targeted lung health check scheme. A successful test phase, in which 76% of lung cancers in those tested were caught at an earlier stage, led to the decision to roll out the targeted screening programme on a national level. People aged 55 to 74 with a GP record including a history of smoking will be assessed and invited for screenings and smoking cessation services.(29)

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Although outcomes are more favourable for early stage lung cancer, a proportion of patients will recur after surgery (30%–55% for NSCLC).(17) Onset of postoperative recurrence for lung cancer is rapid, with 50–90% of cases presenting within 2 years after the operation, and 90–95% manifest within 5 years.(30) Risk of recurrence is higher with increasing stage of the primary lung cancer. Moreover, most recurrences present as distant metastases.(31-33) One study reported recurrence rates of 17% for local sites, 44% for distant sites and 39% for both local and distant.(34) Thus, there remains an unmet need for novel treatments to reduce the risk of recurrence and improve survival for those whose cancers are identified early, more of whom are likely to be identified with the introduction of the targeted lung cancer screening programme.

Table 5. Cancer survival in England by stage at diagnosis patients diagnosed between 2016 and 2020 and followed up to 2021(28)

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

Abbreviation: N/A: not applicable.

B.1.3.2. Treatment pathway and proposed positioning of the technology

The National Institute for Health and Care Excellence has produced a guideline on the diagnosis and management of lung cancer — NICE Guideline 122 (NG122).(3) As outlined in NG122, considerations when deciding on the most appropriate treatment strategy for a patient who has been newly diagnosed with potentially resectable NSCLC are the stage of disease and the operability of the patient.(3) For resectable NSCLC, NG122 recommends surgery, radiotherapy, chemotherapy, or a combination of these interventions.(3) As discussed earlier, targetable mutations (e.g., EGFR or ALK) are also a consideration, but more commonly in the adjuvant setting and for those with locally advanced or metastatic disease at diagnosis. Although testing for biomarkers is not yet routine practice in the neoadjuvant setting, the availability of treatments for which the Blueteq recommends testing for mutations ahead of treatment (e.g., neoadjuvant nivolumab in NSCLC [EGFR and ALK]) means this is a dynamic landscape that is expected to result in the increased use of biomarker tests to guide therapy decisions in the neoadjuvant setting. However, there may be instances where, to avoid delays, patients are treated before the results of the investigations are available.

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Initially, those with NSCLC that is deemed to be resectable are evaluated to determine whether treatment is being given with curative intent.(3) Cardiovascular and lung function are assessed, and, if a person is deemed to be a candidate for curative intent, NG122 recommends surgical resection as the preferred treatment option, specifically lobectomy (either open or thoracoscopic). Post-operative cisplatin-based chemotherapy is an option for those who are sufficiently fit (WHO performance status of 0 or 1) and whose tumours met specific TNM categorisations before surgery (Figure 2):(3) TNM categories eligible for adjuvant chemotherapy are T1a–4, N1–2, M0 and T2b–4, N0, M0 with tumours greater than 4 cm in diameter. For locally advanced tumours (stage IIIA–N2) that are deemed operable, if the patient is fit enough, NG122 recommends combining surgery with chemoradiotherapy, and that surgery be scheduled for 3 to 5 weeks after the chemoradiotherapy. Although chemoradiotherapy is recommended by NICE as an option for stage IIIA–N2 tumours, MSD has received feedback from clinical experts that chemoradiotherapy in combination with surgery is rarely used in clinical practice for this tumour staging. Therefore, MSD do not consider chemoradiotherapy to be a relevant comparator for pembrolizumab in the peri-adjuvant setting (more detail is provided in the discussion of the decision problem; Table 1).

For those with stage I–IIA (T1a–T2b, N0, M0) NSCLC who decline lobectomy or for whom it is contraindicated, NG122 advises offering radical radiotherapy with stereotactic ablative radiotherapy (SABR) or sublobar resection (Figure 2). Conventional or hyperfractionated radiotherapy are alternative options for those contraindicated to SABR. Radical radiotherapy without surgery can be given with curative intent. Chemoradiotherapy is an option for those with stage II or III NSCLC who are not suitable for or who decline surgery.

NG122 currently recommends against the use of neoadjuvant chemotherapy for people with stage I–II NSCLC who are suitable for surgery, unless given as part of a clinical trial. However, subsequent to the last update of NG122 in 2019, NICE recommended nivolumab in combination with chemotherapy as an option for the neoadjuvant treatment of resectable NSCLC of at least 4 cm or node positive in adults (stage IIA–IIIB [N2] based on 8th edition of AJCC/UICC system; Figure 2).(7)

Data compiled by the NHS on treatments for NSCLC indicate that, in 2020, of those assessed as having stage I lung cancer, 44.5% underwent surgical resection alone, with the next most commonly received treatments being other care (29.8%) and radiotherapy alone (22.0%):(35) chemoradiotherapy and surgery in combination with another modality were received by <1%. By contrast, of those with stage III NSCLC, 39.4% received other care, with the next most common treatment being chemoradiotherapy (18.9%).

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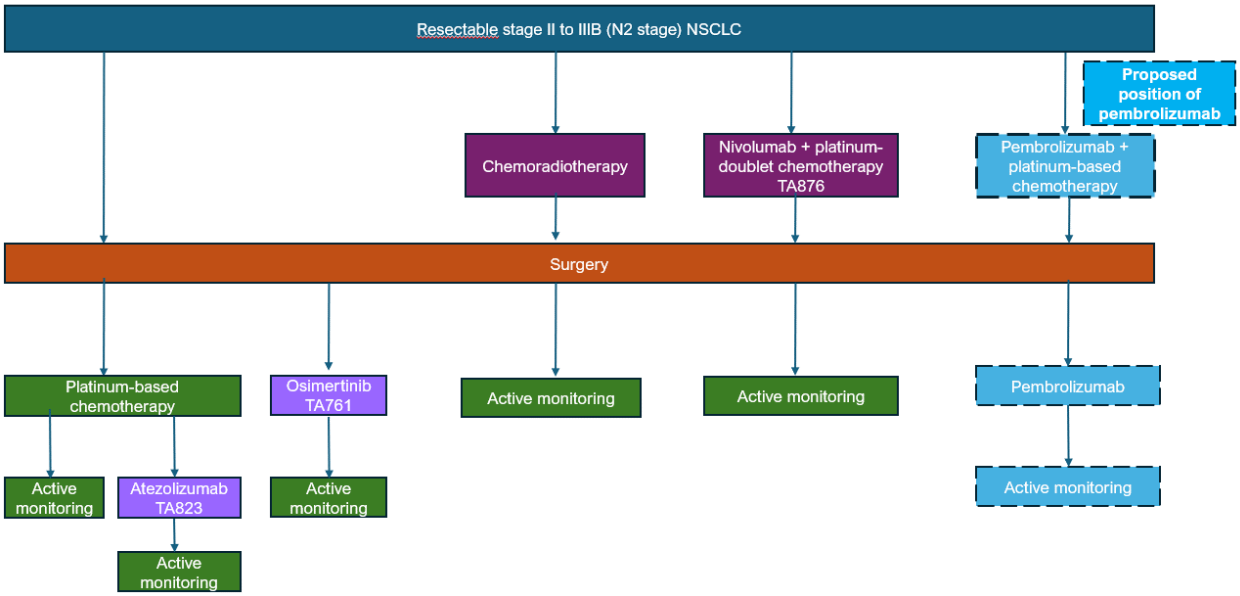
After treatment, patients are monitored for recurrence, undergoing CT scans at regular intervals of 3–6 months after initial treatment, with decreasing frequency of scans after 1 year of no evidence of recurrent disease.(36)

Figure 2. Treatment pathway for resectable NSCLC and potential position of peri-adjuvant pembrolizumab



Note: Atezolizumab and osimertinib are available through the Cancer Drugs Fund. Osimertinib is recommended for adjuvant use after complete resection in those who carry the EGFR mutation. Atezolizumab is recommended for adjuvant use in those with PD-L1 TPS ≥50%.

Abbreviations: EGFR, Epidermal growth factor receptor; NSCLC, Non-small cell lung cancer; PD-L1, Programmed death-ligand 1; TPS, Tumour proportion score.

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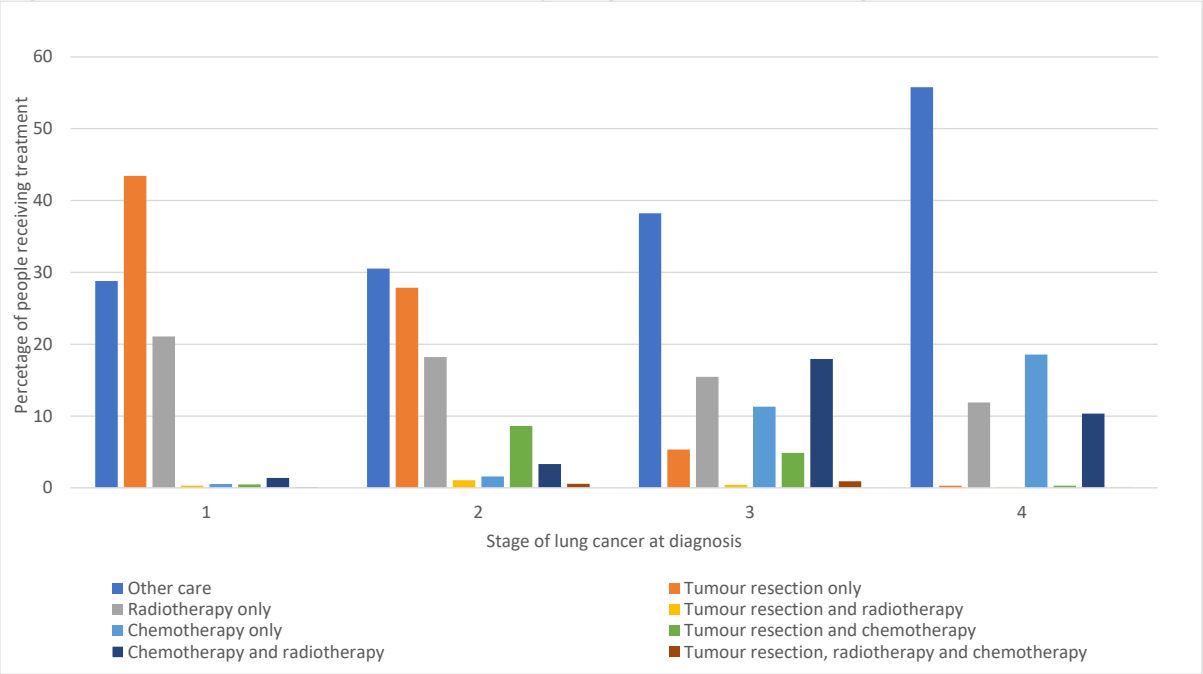
Figure 3. First-line treatments received by stage of NSCLC at diagnosis (2020)



Source is CancerData with criteria selected of NSCLC, stage at diagnosis, and year of 2020.(35)

The goal of systemic treatment in resectable disease is to maximise the possibility of achieving and maintaining a cancer-free state.(37-39) In the neoadjuvant setting, systemic treatments are given to stop the growth of any micro-metastases already circulating in the body. Immunotherapies, such as pembrolizumab, by their mode of action, reactivate the patient's immune system thereby not only amplifying the response against micro-metastases but also against tumour cells potentially released during surgery. Systemic adjuvant treatments are given to eliminate any distant micro-metastases that might remain after surgery. In the peri-adjuvant setting, which is the proposed positioning of pembrolizumab (Figure 2), systemic treatment is given both before and after surgery.

Clinical experts consulted by MSD recommended that patients are seen by an oncologist before a surgeon, to discuss the patient's preference for either having neoadjuvant treatment or moving straight to surgery:[(35)] clinical experts commented that patient preference in many cases is to undergo surgery before any prior treatment, particularly when their surgeon does not want to provide neoadjuvant therapy. Clinical experts commented that they would prioritise incorporating neoadjuvant therapy into the treatment plan of patients with stage III NSCLC as these patients are likely to most benefit from neoadjuvant treatment, but will also consider those with stage II NSCLC.[(35)] However, clinical experts also stressed that they would like the option of adding adjuvant immunotherapy to a patient's treatment plan,

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particularly for those patients whom they consider at higher risk of recurrence, a strategy that is not available with neoadjuvant nivolumab plus chemotherapy.

Use of immunotherapies in early stage NSCLC is an emerging field, and there are some uncertainties to be addressed. A head-to-head clinical trial comparing neoadjuvant versus peri-adjuvant immunotherapy has not been carried out. Clinicians have highlighted that the extent of the additional clinical benefit of peri-adjuvant treatment is uncertain and that they would aim to avoid overtreating patients who may receive limited extra benefit of adjuvant treatment. At the time of writing, there are no NICE recommended peri-adjuvant immunotherapy treatments for early stage NSCLC, but there are three technology appraisals ongoing for peri-adjuvant immunotherapy: durvalumab,(40) nivolumab,(41) and pembrolizumab.(2) Should peri-adjuvant immunotherapies be recommended by NICE, unlike the metastatic setting, criteria are not available to guide clinicians as to which patients would be suitable for neoadjuvant immunotherapy alone versus peri-adjuvant treatment.

One factor that has the potential to inform the choice of augmenting treatment with adjuvant immunotherapy is whether or not a patient achieved a pathological complete response (pCR) after surgery, which is defined as the absence of residual viable tumour as determined by histopathologic assessment of tissue samples taken during surgery; pCR as an outcome was captured in KEYNOTE-671. A recent systematic review evaluating the association of pCR and survival outcomes from clinical studies evaluating neoadjuvant treatment in early stage NSCLC concluded that pCR after neoadjuvant chemotherapy with or without radiotherapy is associated with significant improvements in survival outcomes.(42) Therefore, those not achieving pCR could be considered for continued immunotherapy in the adjuvant setting, whereas those with a pCR would likely require no further treatment, which mitigates concerns about potentially unnecessarily exposing patients to risk of adverse effects.(36) Clinical advisors consulted by MSD agreed that treatment should be stopped for patients who achieve pCR after surgery. No treatment in the adjuvant setting aligns with the decision problem subgroup “whether pembrolizumab is used before or after surgery” and, therefore, the strategy is explored in scenario analyses.

In early stage NSCLC, before the introduction of neoadjuvant immunotherapy, about 4% of patients achieved pCR,(43) as observed in the control groups of recently conducted clinical studies.(20, 44, 45) In the same clinical trials, the proportion of patients achieving pCR in the group receiving immunotherapy (in combination with chemotherapy) ranged from 17% to 24%.(20, 44, 45) Neoadjuvant immunotherapy is associated with improved pCR in early stage NSCLC, and, therefore, likely more favourable prognosis for the longer term. However,

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about 80% of patients do not achieve pCR and remain at high risk of recurrence of their disease. Having adjuvant treatment with pembrolizumab as an option would improve the probability of favourable outcomes for patients with and without pCR.

In summary, despite the recent advances in the management of early stage NSCLC, MSD consider that there remains a need for new therapies to ensure that patients and clinicians have as wide a selection of treatment options available to them as possible. Introduction of peri-adjuvant pembrolizumab into the treatment pathway would be a further advance in the treatment of resectable NSCLC.

B.1.4. Equality considerations

No equity or equality considerations are anticipated.

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B.2. Clinical effectiveness

- **Summary of key clinical effectiveness information**
- ***Randomised controlled trial:***
- KEYNOTE-671, is a phase III randomised, double-blind trial of pembrolizumab in combination with platinum doublet neoadjuvant chemotherapy before surgery, followed by pembrolizumab alone after surgery in participants with resectable II, IIIA and resectable IIIB N2 NSCLC. It included 10 patients across 5 UK trial sites.
- The data presented below is the from the latest Interim Analysis, IA2, which had a data cut off of 10th July 2023.
- Median EFS was approximately 29 months longer in the pembrolizumab arm compared with the placebo arm, with a hazard ratio of 0.59 (95% confidence interval [CI]: 0.48 to 0.72), representing a 41% reduction in risk of an event.
- OS was found to have a statistically significant improvement in the pembrolizumab arm with a hazard ratio of 0.72, representing a 28% reduction in the risk of death. Median OS in the pembrolizumab arm had not been reached at the time of the IA2 data cut off.
- The results from the EQ-5D-5L at neoadjuvant week 11 and adjuvant week 10 showed [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. Most AEs were Grade 1 or 2.
- ***Network meta-analysis****:*
- Constant HRs and time-varying NMAs for the outcome of EFS were carried out to compare peri-adjuvant pembrolizumab versus comparators listed in the NICE decision problem and considered relevant by MSD.
- RCTs informing the NMA were identified by an SLR and an NMA feasibility assessment was performed.
- The results of the time-varying NMA, which informs MSD's base case in the evaluation of cost effectiveness, indicated that peri-adjuvant pembrolizumab was statistically significantly more clinically effective than neoadjuvant chemotherapy

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and surgery alone at all discrete timepoints. HRs at 48 months from MSD's preferred model:

    - Versus surgery alone: HR 0.48 (95% CrI: 0.32 to 0.70);
    - Versus neoadjuvant chemotherapy: HR 0.49 (95% CrI: 0.36 to 0.66).

- No statistically significant differences were observed between peri-adjuvant pembrolizumab and neo-adjuvant nivolumab at any time point, although the magnitude of relative treatment effect increased steadily in favour of pembrolizumab across the time horizon. HR at 48 months from MSD's preferred model:
    - Versus neoadjuvant nivolumab: HR 0.61 (95% CrI: 0.34 to 1.10).
- In terms of direction of effect and statistical significance, the results of the time-constant HR NMA were similar to the results of the time-varying HR NMA: pembrolizumab remained clinically more effective than neoadjuvant chemotherapy and surgery alone. No statistically significant differences were observed between peri-adjuvant pembrolizumab and neoadjuvant nivolumab.

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 and select relevant evidence on the efficacy and safety of pembrolizumab and any comparator treatments for the indication of interest for this appraisal. As the manufacturer of pembrolizumab, MSD are aware of all relevant clinical trials for pembrolizumab in the relevant indication. Full details of the SLR methodology followed to identify and select the clinical evidence relevant to the technology being evaluated are provided in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

The SLR retrieved 3,507 unique records, from which one randomised controlled trial (RCT) — KEYNOTE-671(20, 46) — was identified that provided evidence of the clinical effectiveness and tolerability profile of pembrolizumab in the patient population relevant to this appraisal (Table 6).

Table 6. Clinical effectiveness evidence: KEYNOTE-671

Study	KEYNOTE-671 (NCT03425643)
Study design	Phase III, randomized and double-blind

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Population	Adults aged 18 or over with resectable stage II, IIIA, or IIIB (T3/4N2) NSCLC
Intervention(s)	**Neoadjuvant phase** Pembrolizumab in combination with cisplatin plus gemcitabine or pemetrexed **Adjuvant phase** Pembrolizumab
Comparator(s)	**Neoadjuvant phase** Placebo in combination with cisplatin plus gemcitabine or pemetrexed **Adjuvant phase** 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	**Primary outcomes** **Event-free survival (EFS)** Overall survival (OS) **Secondary outcomes** Pathological complete response (pCR) Major pathological response (mPR) Health-related quality of life (HRQoL) assessed by EORTC QLQ-C30
All other reported outcomes	EQ-5D-5L, EORTC LC-13

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol-5D-5L; NSCLC, Non-small cell lung cancer; QLQ-C30, Core quality-of-life questionnaire.

B.2.3. Summary of methodology of KEYNOTE-671

An overview of the methodology of KEYNOTE-671 is presented in Table 7 and additional details are provided in the sections that follow. Hereafter, unless discussing separately the neoadjuvant or adjuvant phase of KEYNOTE-671, the intervention and comparator arms of KEYNOTE-671 are referred to as the pembrolizumab and placebo arms, respectively.

Table 7. Summary of trial methodology

Study name	KEYNOTE-671 (NCT03425643)
Trial design	Phase III, randomized and double-blind

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Eligibility criteria for participants	Inclusion criteria
	• Male/female participants who were at least 18 years of age on the day of informed consent with previously untreated and pathologically confirmed resectable Stage II, IIIA, or IIIB (N2) NSCLC (AJCC Version 8).
	• Lymph node disease required pathologic confirmation, while T3 (rib destruction) disease required only radiographic documentation. A PET scan could be utilized as a surrogate for pathologic staging of N1 lymph nodes for participants with T2b and T4 tumours (the presence or absence of tumour in the N1 lymph nodes did not change the actual stage by which the participant was stratified). Similarly, biopsy confirmation of N2 disease was not required for pathologically confirmed T3N1 tumours and T4N0-1 tumours, as knowledge of the N2 status would not change the stage.
	• Able to undergo protocol therapy, including necessary surgery.
	• Had an ECOG performance status of 0 to 1 within 10 days of randomization.
	• Had adequate organ function as defined in the study protocol.
	Exclusion criteria
	• Had one of the following tumour locations/types:
	  • NSCLC involving the superior sulcus;
	  • Large cell neuro-endocrine cancer;
	  • Sarcomatoid tumour.
	• Had a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or had current pneumonitis/interstitial lung disease that required steroids.
	• Had active autoimmune disease that had required systemic treatment in the past 2 years.
	• Had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another coinhibitory T-cell receptor.
	• Had received prior systemic anticancer therapy including investigational agents for the current malignancy prior to randomization.

Settings and locations where the data were collected	A multinational multicentre study conducted at 189 centres in 25 countries. Ten patients across five UK sites were randomised in KEYNOTE-671.
Trial drugs	**Intervention arm** Neoadjuvant phase: • Pembrolizumab 200 mg every 3 weeks (Q3W) for 4 cycles. • Plus cisplatin 75 mg/m^2 Q3W for 4 cycles. Plus **either**

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	• gemcitabine (squamous tumours) 100 mg/m^2, days 1 and 8 of each 21 day cycle for 4 cycles **OR** • pemetrexed (non-squamous tumours) 500 mg/m^2 Q3W for 4 cycles Adjuvant phase: • Pembrolizumab 200 mg Q3W for 13 cycles. **Comparator arm** Neoadjuvant phase • Placebo (saline) 200 mg Q3W for 4 cycles. • Plus cisplatin 75 mg/m^2 Q3W for 4 cycles. Plus **either** • gemcitabine (squamous tumours) 100 mg/m^2, days 1 and 8 of each 21 day cycle for 4 cycles **OR** • pemetrexed (non-squamous tumours) 500 mg/m^2 Q3W for 4 cycles Adjuvant • Placebo (saline) Q3W for 13 cycles
Primary outcomes	• EFS assessed by a local pathologist or by investigator-assessed imaging using RECIST 1.1. • OS
Other outcomes used in the economic model/specified in the scope	• mPR. • pCR as defined as ypT0/Tis ypN0. • Health utilities assessed using EQ-5D-5L.
Pre-planned subgroups	Age category: • <65, ≥65; • <65, 65–74, 75–84. Gender: • Male, female. Race: • White, all others. Overall cancer staging: • II, III. Region: • Europe, ex Europe; • East Asia, Non-East Asia. Histology: • Squamous, non-squamous. PD-L1 expression level, TPS: • ≥50%, <50%;

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	• ≥1%, <1%; • ≥50%, 1–49%, <1%. Smoking status • Never, former, current. ECOG • 0, 1. EGFR activating mutation status • Yes, no, unknown/missing. ALK translocation status • No, unknown/missing.

Abbreviations: ALK, Anaplastic lymphoma kinase; AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; EFS, Event-free survival; EGFR, Epidermal growth factor receptor; EQ-5D-5L, EuroQol-5D-5L; mPR, Major pathological response; NSCLC, Non-small cell lung cancer; OS, Overall survival; pCR, Pathological complete response; PD-L1, Programmed death-ligand 1; PET, Positron emission tomography; TPS, Tumour proportion score.

B.2.3.1. Trial design

KEYNOTE-671 is an ongoing, Phase 3, randomized, multicentre, double-blind, placebo-controlled study (Figure 4). KEYNOTE-671 compares concomitant neoadjuvant platinum-doublet chemotherapy plus pembrolizumab (every 3 weeks [Q3W] × 4 cycles) followed by surgery and adjuvant pembrolizumab (Q3W × 13 cycles) versus concomitant neoadjuvant platinum-doublet chemotherapy plus placebo (Q3W × 4 cycles) followed by surgery and adjuvant placebo (Q3W × 13 cycles) in participants with resectable stage II or IIIA/B (T3-4N2) NSCLC (Table 7). Platinum-based chemotherapy comprised cisplatin plus either gemcitabine or pemetrexed depending on tumour histology.

Participants were expected to undergo a potentially curative surgical resection that was performed as part of the local standard of care. The maximum interval from the first dose of neoadjuvant therapy to surgery was 20 weeks. If the participant received fewer than 4 cycles of neoadjuvant therapy, surgery was to be carried out within 4–8 weeks after the last dose of therapy (Figure 5). If a participant did not undergo surgery due to refusal, physician decision, medical illness, or any reason other than local progression or metastatic disease, they received radiotherapy (within 8 weeks of day 1 of the last neoadjuvant treatment cycle) and continued to the adjuvant phase. Participants with microscopic residual disease or gross residual disease in the tumour bed after surgery underwent radiotherapy, with radiotherapy starting no earlier than 4 weeks and no later than 8 weeks after surgery (Figure 5). Participants who underwent radiotherapy were to begin adjuvant treatment no earlier than 2 weeks and no later than 4 weeks after completion of radiotherapy.

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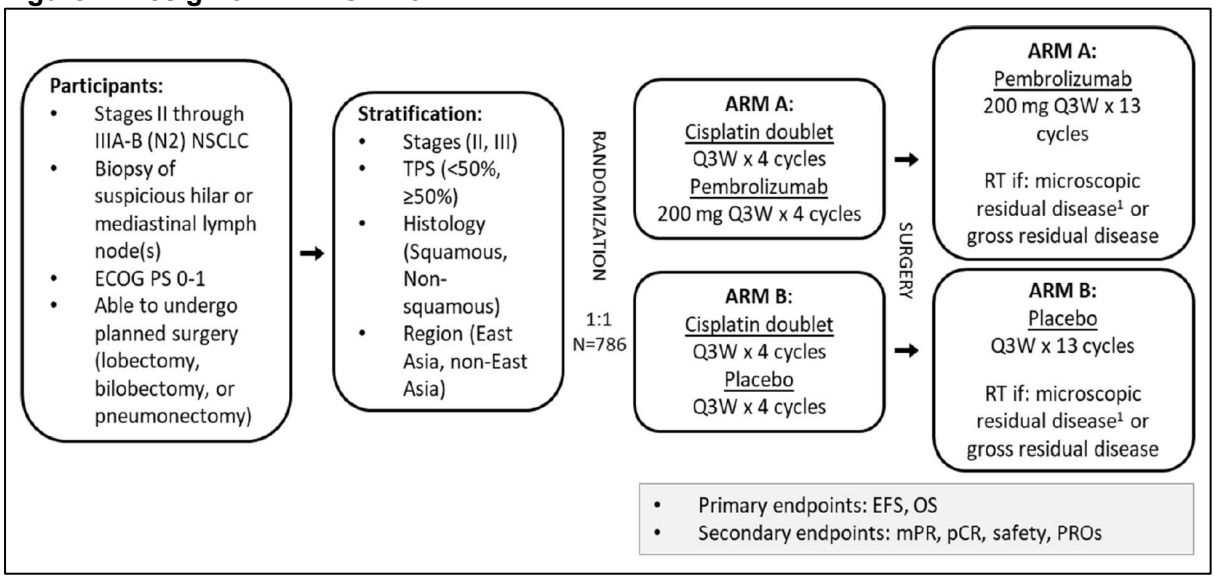
Assessment of surgical margins was performed by the local pathologist on all specimens removed during surgery. Samples of tumour tissue collected from participants during the study were submitted to the designated central laboratory for blinded pathological response assessment.

In the neoadjuvant phase, imaging assessments were carried out (±7 day window):

- 3 weeks after cycles 2 and 4, if patient received all 4 cycles;
- 3 weeks after cycle 2 and 4 weeks after cycle 3, if patient received 3 cycles;
- 3 weeks after cycle 2, if patient received 2 cycles;
- 3 weeks after cycle 1, if patient received 1 cycle.

After surgery, patients underwent new baseline imaging within 4 weeks before the start of their allocated adjuvant treatment, and then every 16 weeks (±14 days) from the date of randomization during year 1, every 16 weeks (±21 days) during years 2 and 3, and every 6 months (±28 days) during years 4 and 5. Participants who did not undergo surgery and did not receive radiotherapy were not required to have new baseline imaging and were to have follow-up scans every 16 weeks (±21 days) from the date of randomization. All imaging assessments were evaluated by the investigator and submitted for blinded independent central review (BICR).

Figure 4. Design of KEYNOTE-671



Note: The schematic depicts the planned number of patients to be randomised (N=786) rather than the number of people recruited to and randomised in KEYNOTE-671.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EFS, Event-free survival; mPR, Major pathological response; NSCLC, Non-small cell lung cancer; OS, Overall survival; pCR, Pathological complete response; PRO, Participant-reported outcomes; PS, Performance status; Q3W, Every 3 weeks; RT, Radiotherapy; TPS, Tumour proportion score.

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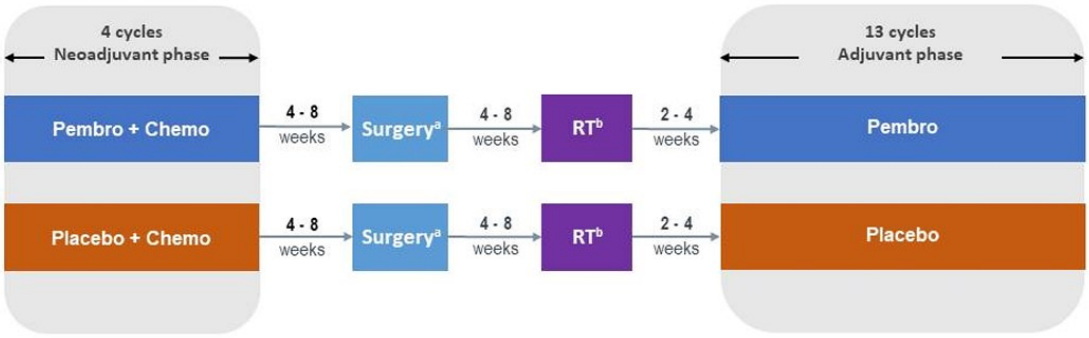
Figure 5. Phases and timings of KEYNOTE-671



[a] If a participant did not undergo surgery due to refusal, physician decision, medical illness, or any reason other than local progression or metastatic disease, they were to receive radiotherapy and continue to the adjuvant phase.

[b] Only participants with microscopic residual disease or gross residual disease in the tumour bed after surgery were to undergo radiotherapy.

B.2.3.2. Assignment, randomisation, and blinding

Treatment allocation occurred centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). KEYNOTE-671 enrolled 797 participants who were randomized in a 1:1 ratio to the pembrolizumab and placebo groups.

Randomization was stratified by:

1. Stage (II, III);
2. TPS (<50%, ≥50%);
3. Histology (squamous, non-squamous);
4. Region (East Asia, non-East Asia).

Pembrolizumab and placebo appeared identical so that masking to treatment was maintained. The participant, the investigator and Sponsor personnel or delegate(s) who were involved in the study treatment administration or clinical evaluation of the participants were unaware of the group assignments.

B.2.3.3. Eligibility criteria

Key eligibility criteria are provided in Table 7. A full list of eligibility criteria is available in Appendix E.

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B.2.3.4. Settings and locations where the data were collected

KEYNOTE-671 is a multinational multicentre study that was conducted at 189 centres in 25 countries covering Europe, East Asia, North America and South America (Table 8). Ten patients from the UK were randomized across five sites.

Table 8. KEYNOTE-671 countries with trial sites, by region

Europe	East Asia	Other
Belgium	China	Argentina
Estonia	Japan	Australia
France	Republic of Korea	Brazil
Germany	Malaysia	Canada
Ireland	Taiwan	Russian Federation
Latvia		South Africa
Lithuania		Ukraine
Poland		United States
Romania		
Spain		
United Kingdom		

B.2.3.5. Trial drugs and concomitant medications

Pembrolizumab, placebo and chemotherapy were administered until the maximum number of cycles was reached or until disease progression or recurrence, the occurrence of unacceptable toxic effects, a decision by the investigator to stop administration, withdrawal of consent, or other reasons (see CONSORT diagram in Appendix D): treatment doses and schedules are presented in Table 9. Patients who discontinued study treatment prior to completion of the protocol-specified treatment period continued to participate and to be monitored unless they withdrew from the trial.

Table 9. KEYNOTE-671 trial drugs

Component	Treatment	Unit dose strength(s)	Dosage level(s)	Route of administration	Treatment period
Neoadjuvant phase					
Pembrolizumab	Pembrolizumab	25 mg/mL	200 mg	IV infusion	Day 1 of each 21 day cycle for 4 cycles
Placebo	Normal saline	N/A	N/A	IV infusion	Day 1 of each 21 day cycle for 4 cycles
Chemotherapy	Cisplatin	1 mg/mL	75 mg/m^2	IV infusion	Day 1 of each 21-day cycle for 4 cycles

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	Gemcitabine (squamous tumours)	1000 mg/vial	1000 mg/m^2	IV infusion	Day 1 and Day 8 of each 21-day cycle for 4 cycles
	Pemetrexed (non-squamous tumours)	500 mg/vial	500 mg/m^2	IV infusion	Day 1 of each 21-day cycle for 4 cycles
Adjuvant phase					
Pembrolizumab	Pembrolizumab	25 mg/mL	200 mg	IV infusion	Day 1 of each 21 day cycle for 13 cycles
Placebo	Normal saline	N/A	N/A	IV infusion	Day 1 of each 21 day cycle for 13 cycles

Abbreviations: IV, Intravenous; N/A, Not applicable.

All treatments that the investigator considered necessary for a participant's welfare were allowed, at the discretion of the investigator and in keeping with the community standards of medical care.

The following medicines were prohibited:

1. Antineoplastic systemic chemotherapy or biological therapy;
2. Immunotherapy not specified in the protocol;
3. Chemotherapy not specified in the protocol;
4. Radiation therapy not specified in the protocol;
5. Investigational agents other than pembrolizumab;
6. Live vaccines within 30 days prior to the first dose of trial treatment and while receiving study treatment. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and were not allowed;
7. Systemic corticosteroids except for AE management;
8. For participants receiving radiotherapy, prophylactic growth factor support such as erythropoietin or granulocyte-colony stimulating factor is not permitted while receiving radiotherapy.

B.2.3.6. Outcomes assessed

B.2.3.6.1. Primary outcomes

KEYNOTE-671 had co-primary endpoints of EFS (investigator assessed) and OS.

EFS is defined as the time from randomization to the first of the following events:

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- radiographic disease progression per RECIST 1.1 for participants who did not have surgery;
- local progression precluding planned surgery;
- inability to resect tumour;
- local or distant recurrence;
- death.

EFS was biopsy assessed by a local pathologist or by investigator-assessed imaging using RECIST 1.1. It is noted that all imaging assessments were evaluated by the investigator and submitted for BICR.

OS is defined as the time from randomization to death due to any cause.

B.2.3.6.2. Secondary outcomes

Data on three secondary outcomes were captured in KEYNOTE-671:

- pCR in the resected primary tumour and lymph nodes
    - Assessed by blinded central laboratory pathologist after neoadjuvant pembrolizumab/placebo plus chemotherapy;
    - Defined as the absence of residual invasive cancer on haematoxylin and eosin-stained slides of the resected lung specimen and lymph nodes after completion of neoadjuvant therapy (i.e., ypT0/Tis ypN0).
- mPR
    - Assessed by blinded central laboratory pathologist after neoadjuvant pembrolizumab/placebo plus chemotherapy;
    - Defined as ≤10% viable tumour cells in the resected primary tumour and all resected lymph nodes.
- QoL
    - Assessed via the EORTC QLQ-C30 (items 29 and 30) and EORTC QLQ-LC13;
    - EQ-5D-5L was captured as an exploratory outcome.

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B.2.3.7. Pre-planned subgroups

To determine whether the treatment effect was consistent across subgroups, the between group treatment effect (with a nominal 95% CI) for the primary endpoint was estimated and plotted by treatment group within each category of the following classification variables:

- Tumour stage (II, III);
- TPS (<50%, ≥50%);
- Histology (squamous, non-squamous);
- Geographic region (East Asia, non-East Asia);
- Age category (<65, ≥65 years);
- Sex (female, male);
- Race (white, non-white);
- Smoking status (never, former, current);
- Known EGFR activating mutation status (yes, no);
- ALK translocation status (yes, no).

The consistency of the treatment effect was assessed descriptively via summary statistics by category for the classification variables listed above. If any level of a subgroup variable had fewer than 30 participants, the analysis may not have been performed for that level of the subgroup variable. If a subgroup variable had two levels and one level of the subgroup variable had fewer than 30 participants, then this subgroup may not be displayed in the forest plot. Subgroup analyses for efficacy endpoints were conducted using unstratified methods.

B.2.3.8. Baseline characteristics of trial participants

Demographic and baseline characteristics were generally well balanced between the treatment arms (Table 10). Median age of participants was 64 years, and most participants were male (70.6%) and had stage III NSCLC (70.0%). More than 60% of participants were White (61.4%), former smokers (62.4%), and had ECOG PS 0 (62.6%). PD-L1 expression indicated by TPS ≥50% versus <50% was similar between the treatment arms. With the exception of age, the baseline characteristics of the population enrolled in KEYNOTE-671 are representative of patients in England and Wales likely to be eligible for treatment with pembrolizumab in the setting relevant to this technology appraisal. Considering age, participants enrolled in KEYNOTE-671 are overall younger than the typical patient

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diagnosed with early stage NSCLC. In the UK, highest rates of NSCLC are reported in the 75 to 79 age group for females and the 85 to 89 age group for males.(16) However, it is usual for clinical trials to enrol a cohort that is younger than the average patient who would receive the treatment in clinical practice.

Table 10. Patient characteristics (ITT population)

	Pembrolizumab[a]		Placebo[a]		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	397		400		797	
Sex						
Male	279	70.3	284	71	563	70.6
Female	118	29.7	116	29	234	29.4
Age (years)						
<65	221	55.7	214	53.5	435	54.6
≥65	176	44.3	186	46.5	362	45.4
65–74	153	38.5	152	38	305	38.3
75–84	23	5.8	34	8.5	57	7.2
Mean	62.7		63.6		63.1	
SD	8.5		8.1		8.3	
Median	63		64		64	
Range	26 to 83		35 to 81		26 to 83	
Race						
American Indian or Alaska Native	1	0.3	0	0	1	0.1
Asian	124	31.2	125	31.3	249	31.2
Black or African American	6	1.5	10	2.5	16	2
Multiple	3	0.8	10	2.5	13	1.6
Black or African American	3	0.8	10	2.5	13	1.6
White	250	63	239	59.8	489	61.4
Missing	13	3.3	16	4	29	3.6
Ethnicity						
Hispanic or Latino	36	9.1	34	8.5	70	8.8
Not Hispanic or Latino	329	82.9	333	83.3	662	83.1
Not Reported	18	4.5	25	6.3	43	5.4
Unknown	14	3.5	8	2	22	2.8
Region (EU vs Ex EU)						
EU	136	34.3	131	32.8	267	33.5
Ex EU	261	65.7	269	67.3	530	66.5
Region (East-Asia vs Non-East Asia)						
East-Asia	123	31	121	30.3	244	30.6

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Non-East Asia	274	69	279	69.8	553	69.4
Overall cancer staging at baseline						
II	118	29.7	121	30.3	239	30
III	279	70.3	279	69.8	558	70
IIIA	217	54.7	225	56.2	442	55.5
IIIB	62	15.6	54	13.5	116	14.6
PD-L1 expression level (50% cutoff)						
TPS ≥50%	132	33.2	134	33.5	266	33.4
TPS <50%	265	66.8	266	66.5	531	66.6
PD-L1 expression level (1% cutoff)						
TPS ≥1%	259	65.2	249	62.3	508	63.7
TPS <1%	138	34.8	151	37.8	289	36.3
PD-L1 expression level						
TPS ≥50%	132	33.2	134	33.5	266	33.4
TPS 1–49%	127	32	115	28.8	242	30.4
TPS <1%	138	34.8	151	37.8	289	36.3
Smoking status						
Never smoker	54	13.6	47	11.8	101	12.7
Former smoker	247	62.2	250	62.5	497	62.4
Current smoker	96	24.2	103	25.8	199	25
Baseline ECOG						
0	253	63.7	246	61.5	499	62.6
1	144	36.3	154	38.5	298	37.4
Histology						
Squamous	171	43.1	173	43.3	344	43.2
Non-squamous	226	56.9	227	56.8	453	56.8
EGFR activating mutation status						
Yes	14	3.5	19	4.8	33	4.1
No	111	28	124	31	235	29.5
Unknown/missing	272	68.5	257	64.3	529	66.4
ALK translocation status						
Yes	12	3	9	2.3	21	2.6
No	104	26.2	132	33	236	29.6
Unknown/missing	281	70.8	259	64.8	540	67.8

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

Data presented based on database cutoff of 10 July 2023.

Abbreviations: ALK, Anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, Epidermal growth factor receptor; EU, Europe; ITT, Intention to treat; PD-L1, Programmed death-ligand 1.

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B.2.4. Statistical analysis and definition of study groups in KEYNOTE-671

B.2.4.1. Objectives, hypotheses, and endpoints

The statistical methods used to evaluate primary and secondary efficacy endpoints for KEYNOTE-671 are summarised in Table 11.

For both EFS and OS, the non-parametric Kaplan–Meier (KM) method was used to estimate the survival curves in each treatment group. The treatment difference in EFS and OS between treatment arms was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the two study groups. The hazard ratio and its 95% CI from the stratified Cox model with a single treatment covariate is reported for both outcomes. For OS, participants without documented death at the time of analysis were censored at the date of last known contact: for censoring rules applied in the analysis of EFA, please see Table 10 of the Clinical Study Report (CSR) for KEYNOTE-671.(47)

The difference between groups in mPR rate and pCR rate was estimated using the stratified Miettinen and Nurminen method with strata weighting by sample size. For mPR and pCR, participants with missing data were considered non-responders. For a more detailed description of the methodologies used and rules applied to generate estimates of treatment effect, please see the CSR for KEYNOTE-671.(47)

Table 11. KEYNOTE-671 study objectives and endpoints

Objective	Endpoint(s)
Primary	
To evaluate EFS by biopsy assessed by a local pathologist or by investigator-assessed imaging using RECIST 1.1	EFS
To evaluate OS	OS
Secondary	
To evaluate the rate of mPR assessed by blinded central laboratory pathologist after neoadjuvant chemotherapy with or without pembrolizumab	mPR
To evaluate the rate of pCR in the resected primary tumour and lymph nodes assessed by blinded central laboratory pathologist after neoadjuvant chemotherapy with or without pembrolizumab	pCR

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To evaluate mean change from baseline in the neoadjuvant phase and in the adjuvant phase in global health status/quality of life (QoL) using the EORTC QoL questionnaire (QLQ)-C30	The QoL is based on the global health status/QoL scale (Items 29 and 30) of the EORTC QLQ-C30
To evaluate the safety and tolerability of neoadjuvant chemotherapy plus pembrolizumab followed by surgery and adjuvant pembrolizumab	• Participant experiencing AEs. • Participant discontinuing study drug due to AEs. • Participant experiencing perioperative complications.
Tertiary/exploratory	
To evaluate changes in health-related QoL assessment from baseline in the neoadjuvant phase and in the adjuvant phase	Change from baseline in health-related QoL evaluated using the multi-item and single-item scales of EORTC QLQ-C30 and EORTC QLQ-LC13 scores: • Physical functioning (EORTC QLQC-30 items 1-5) • Role functioning (EORTC QLQ C30, items 6-7) • Dyspnea (EORTC QLQC30 item 8) • Cough (EORTC QLQ-LC13 item 31) • Chest pain (EORTC QLQ- LC13 item 40)
To characterize health utilities in neoadjuvant and adjuvant phases using EQ-5D-5L	Health utilities assessed using EQ-5D-5L
To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab plus chemotherapy used as neoadjuvant and in combination with pembrolizumab as adjuvant	The relationship between molecular biomarkers and clinical activity that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of the study treatments

Abbreviations: EFS, Event free survival; EORTC, European Organisation for Research and Treatment of Cancer; mPR, Major pathological response; OS, Overall survival; pCR, Pathological complete response; QoL, quality-of-life; QLQ-C30, Core quality of Life questionnaire.

B.2.4.1.1. Analysis populations

Efficacy analysis population

Analyses of the co-primary endpoints of EFS and OS, and of the secondary outcomes of mPR and pCR, were based on the ITT population, which includes all randomized participants who were analysed in the treatment arm to which they were randomized. The ITT population comprised 797 patients.

Analyses of patient reported outcome (PRO) endpoints were conducted using the PRO full analysis set (FAS) population, defined as all randomized participants who had at least 1 PRO assessment available and received at least 1 dose of study intervention (N=749). Participants were analysed in the treatment arm to which they were randomized.

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Safety analysis population

Analyses of safety data were based on the 'all participants as treated' (APaT) population, which included randomized participants who received at least 1 dose of allocated study treatment (N=795). Participants were analysed according to the study intervention they received.

B.2.4.1.2. Sample size considerations

Sample size calculations indicated that 786 participants (i.e., 393 per arm) would be needed to ensure adequate power for the EFS and OS results. Assumptions applied to generate the sample size and power calculations were:

- EFS follows an exponential distribution with a median of 21 months for the control group and 30 months for the experimental group;
- OS follows an exponential distribution with a median of 34 months for the control group and 48.6 months for the experimental group;
- The hazard ratio for EFS and OS between the experimental and control groups is 0.7;
- The enrollment period is 24 months with a ramp up period of 6 months;
- The monthly drop-out rate is 1% for both EFS and OS.

For EFS, based on a target number of ~416 events at interim analysis 2 (IA2: i.e., final analysis for EFS; Table 12), the study has power of 90% to detect a hazard ratio of 0.7 at α=0.01. Power is increased to 94.9% at α=0.025. For OS, based on a target number of [redacted] deaths at final analysis, the study has power of 90% (α=0.0148) or 93.2% (α=0.025) to detect a hazard ratio of 0.7.

Additionally, there is 99.1% power to detect a difference in mPR rates at the allocated α=0.0001, assuming an underlying 22% mPR rate in the placebo arm and 42% in the group receiving pembrolizumab. There is 99.3% power to detect a difference in pCR rates at the allocated α=0.0001, assuming underlying pCR rates of 8% and 24% in the placebo and pembrolizumab groups, respectively.

B.2.4.1.3. Interim and final efficacy analyses

Four interim efficacy analyses and one final analysis were planned for KEYNOTE-671. The planned analyses, endpoints evaluated, and drivers of timing are summarized in Table 12.

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Table 12. Purpose and timing of interim and final analysis

Analyis	Key endpoints	Timing	Purpose
IA1	EFS OS mPR rate pCR rate	~326 EFS events have been observed and ~5 months after last participant was randomized	EFS interim analysis (~78% of target EFS events) OS interim analysis (~41% of target OS events) mPR and pCR rate analyses
IA2	EFS OS	[redacted] EFS events have been observed (~60 months after first participant was randomized)	EFS final analysis OS interim analysis ([redacted]% of target OS events)
IA3	OS	[redacted] deaths have been observed (~72 months after first participant was randomized)	OS interim analysis ([redacted]% of target OS events)
IA4	OS	[redacted] deaths have been observed (~84 months after first participant was randomized)	OS interim analysis ([redacted]% of target OS events)
FA	OS	[redacted] deaths have been observed (~96 months after first participant was randomized)	OS final analysis

Abbreviations: EFS, Event free survival; FA, Final analysis; IA, Interim analysis; mPR, Major pathological response; OS, Overall survival; pCR, Pathological complete response.

Multiplicity

The overall type I error rate over the multiple endpoints was strongly controlled at 2.5% (one-sided) for all hypotheses using the graphical approach of Maurer and Bretz.(48) Initially, a 0.01% (one-sided) type I error rate was allocated to test mPR rate, 0.01% (one-sided) was allocated to test pCR rate,1.0% (one-sided) allocated to test EFS and 1.48% (one-sided) allocated to test OS. The graphical approach of Maurer and Bretz was applied to re-allocate alpha among the hypotheses for mPR rate, pCR rate, EFS and OS. Group sequential methods were used to allocate alpha among the interim and final analyses for the EFS and OS endpoints.

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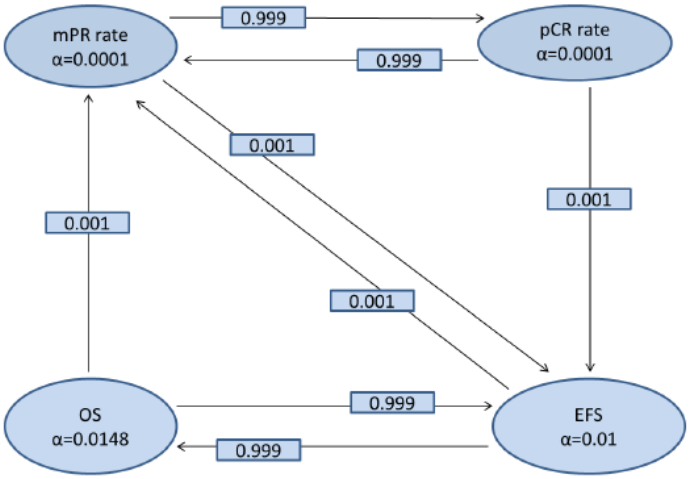
Figure 6. Multiplicity graph for type 1 error control



Note: The initial one-sided α-allocation for each hypothesis is reported in the ellipse representing the hypothesis. The initial weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

B.2.5. Critical appraisal of KEYNOTE-671

A quality assessment of the KEYNOTE-671 trial was performed using the Cochrane risk-of-bias tool for randomised trials (ROB-2),(49) the results of which are presented in Appendix D and demonstrate low risk of bias across all domains. A summary for assessment for risk of bias for the outcome of EFS is provided below (Table 13).

Table 13. KEYNOTE-671 risk of bias assessment

Domain	Risk of bias assessment	Justification
Randomisation process	Low	Randomisation was carried out centrally using an interactive voice response system / integrated web response system. Baseline characteristics were well-balanced between treatment groups.
Deviations from intended interventions	Low	Participants, carers and treating clinician were masked to treatment. Pembrolizumab and placebo were identical in appearance so the blind was maintained.
Missing outcome data	Low	Data are available for all randomized participants. Proportion of participants lost to follow-up was similar between treatment groups.
Measurement of the outcome	Low	Investigators were blinded to treatment allocation. Additionally, imaging assessments were also subject to blinded independent central review.
Selection of the reported result	Low	EFS was a pre-specified co-primary outcome.

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Overall	Low	All domains are assessed as being at low risk of bias.

B.2.6. Clinical effectiveness results of KEYNOTE-671

Data reported here represent the results of the prespecified IA2, with a database cutoff date of 10th July 2023. Results are reported for the ITT population of KEYNOTE-671, which reflects the anticipated licensed population (adults with resectable stage II, IIIA, or IIIB [T3-4N2] NSCLC).(1)

B.2.6.1. Patient disposition and duration of follow-up

Of 1364 people screened for entry into KEYNOTE-671, 797 were randomized to either pembrolizumab or placebo. The median duration of follow up for the ITT population was 29.8 months and was similar between the two treatment arms (31.5 months with pembrolizumab versus 28.9 months with placebo; Table 14). Median follow-up from randomisation to death was 36.6 months.(46)

Table 14. Summary of follow-up duration (ITT population)

Follow-up duration (months)[a]	Pembrolizumab[b] (N=397)	Placebo[b] (N=400)	Total (N=797)
Median (Range)	31.5 (0.4, 61.7)	28.9 (0.6, 62.0)	29.8 (0.4, 62.0)
Mean (SD)	32.0 (15.2)	30.0 (14.2)	31.0 (14.7)

[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive.

[b] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

Database cutoff date 10 July 2023

By the IA2 data cutoff date (10 July 2023), 191 participants (48.2%) allocated to pembrolizumab and 174 (43.6%) allocated to placebo had completed study treatment (Table 15). The most frequent reason for discontinuation of study treatment was adverse effects (AEs: 21.7%) for those receiving pembrolizumab but progressive disease (26.6%) for those in the placebo group. At the time of the data cutoff for IA2, no participant in either arm remained on study treatment. The proportion of participants who discontinued from the trial was larger in the placebo group (30.5% with pembrolizumab versus 38.3% with placebo), with the most common reason for both arms cited as death (27.5% with pembrolizumab versus 35.3% with placebo).

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The proportion of participants not undergoing surgery was similar in the two treatment groups at 17.9% and 20.5% in the pembrolizumab and placebo groups, respectively (Table 15). For those allocated to pembrolizumab, experiencing an adverse event in the neoadjuvant phase was the most common reason for not moving to surgery (35% of those not having surgery), whereas progressive disease was the most common event precluding surgery in the placebo group (32% of those not having surgery).

Table 15. Disposition of participants (ITT population)

	Pembrolizumab[a]	Placebo[a]
	n (%)	n (%)
Participants in population	397	400
Status for study treatment (neoadjuvant/surgery plus adjuvant)		
Started	396	399
Completed	191 (48.2)	174 (43.6)
Discontinued	205 (51.8)	225 (56.4)
Adverse event	86 (21.7)	39 (9.8)
• Associated with COVID-19	3 (0.8)	0 (0.0)
Clinical progression	2 (0.5)	3 (0.8)
Local progression preventing surgery	1 (0.3)	6 (1.5)
Non-study anti-cancer therapy	2 (0.5)	6 (1.5)
• Associated with COVID-19	0 (0.0)	1 (0.3)
Physician decision	22 (5.6)	17 (4.3)
• Associated with COVID-19	1 (0.3)	1 (0.3)
Progressive disease	62 (15.7)	106 (26.6)
Protocol violation	1 (0.3)	1 (0.3)
• Associated with COVID-19	0 (0.0)	1 (0.3)
Tumour found to be surgically unresectable	5 (1.3)	15 (3.8)
Withdrawal by subject	24 (6.1)	32 (8.0)
• Associated with COVID-19	2 (0.5)	0 (0.0)
Status for trial		
Discontinued	121 (30.5)	153 (38.3)
Death	109 (27.5)	141 (35.3)
• Associated with COVID-19	5 (1.3)	4 (1.0)
Lost to follow up	2 (0.5)	0 (0.0)
Withdrawal by subject	10 (2.5)	12 (3.0)
• COVID-19 association unspecified, subsequently died	1 (0.3)	3 (0.8)
Participants ongoing	276 (69.5)	247 (61.8)
In-study surgery		
Underwent surgery	325	317

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Lobectomy	256 (78.8)[d]	238 (75.1)[d]
Bilobectomy	26 (8.0)	26 (8.2)
Pneumonectomy	37 (11.4)	39 (12.3)
Exploratory thoracotomy	4 (1.2)	13 (4.1)
Segmentectomy	1 (0.3)	0
Wedge resection	1 (0.3)	0
Lymph node dissection only	0	1 (0.3)
No in-study surgery		
Did not undergo surgery	71 (17.9)	82 (20.5)
Adverse event	25 (6.3)	17 (4.2)
Clinical progression[b]	1 (0.3)	1 (0.2)
Local progression preventing surgery	1 (0.3)	6 (1.5)
New non-study anti-cancer therapy	0	1 (0.2)
Participant refusal	4 (1.0)	3 (0.8)
Physician decision	15 (3.8)	20 (5.0)
Progressive disease[c]	15 (3.8)	26 (6.5)
Withdrawal of consent	10 (2.5)	8 (2.0)
With in-study surgery and in-study radiotherapy	18 (4.5)	35 (8.8)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.

Study treatment includes study medication, in-study surgery and in-study radiotherapy. Completed indicates the completion of 13 cycles of adjuvant pembrolizumab/placebo.

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

[b] Worsening of clinical status felt to be related to disease progression in the absence of radiographic evidence of disease progression.

[c] Radiographic disease progression.

[d] One participant in the pembrolizumab group and two participants in the placebo group underwent a lobectomy but were found to have metastatic disease upon surgery and thus considered to have unresectable disease.

Database cutoff date 10 July 2023.

B.2.6.2. Primary outcomes

B.2.6.2.1. Event-free survival

The success criterion for the primary EFS hypothesis was met at IA1 (data cut off 29th July 2022), with a p-value that met the prespecified boundary for statistical significance (see appendix E). At IA2, a continued improvement in EFS by investigator assessment was observed in the pembrolizumab arm compared with the placebo arm (HR; 0.59; 95% CI: 0.48 to 0.72; nominal p<0.00001; Table 16). EFS results at IA2 were consistent with the

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primary analysis at IA1. BICR analysis of EFS generated similar results to the primary analysis based on investigator assessment, with an HR of 0.62 (95%CI: 0.51 to 0.76).

Median EFS was approximately 29 months longer in the pembrolizumab arm (47.2 months [95% CI: 32.9 to NR]) compared with the placebo arm (18.3 months [95% CI: 14.8 to 22.1]). Over time, EFS rate was consistently larger in the pembrolizumab group compared with the placebo group. The most frequent type of first EFS event in both arms was progression/recurrence (Table 16).

The KM plot shows that the curve depicting the pembrolizumab arm separates from that of the placebo arm at approximately Month 5 and remains separated over time (Figure 7). The EFS benefit of pembrolizumab over placebo was consistent across all prespecified subgroups, including PD-L1 expression, histology, and disease stage (Figure 8).

Table 16. Analysis of event-free survival based on investigator assessment (ITT population)

Outcome	Pembrolizumab[a] (N=397)	Placebo[a] (N=400)
Number of events, n (%)	174 (43.8)	248 (62.0)
Median EFS, months (95% CI, months)[b]	47.2 (32.9 to NR)	18.3 (14.8 to 22.1)
EFS HR (95% CI)[c]	0.59 (0.48 to 0.72)	
p-value[d]	<0.00001	
EFS rate at various time points (%) (95% CI)		
6 months	87.2 (83.5 to 90.2)	79.9 (75.6 to 83.5)
12 months	73.8 (69.1 to 77.9)	60.8 (55.8 to 65.5)
24 months	61.5 (56.4 to 66.2)	41.4 (36.3 to 46.4)
36 months	54.3 (48.8 to 59.4)	35.4 (30.3 to 40.6)
48 months	48.4 (41.8 to 54.7)	26.2 (20.0 to 32.9)
Type of first event in EFS analysis (n) (%)		
No event	223 (56.2)	152 (38.0)
Event	174 (43.8)	248 (62.0)
Progression/recurrence	118 (29.7)	187 (46.8)
Local progression preventing surgery	1 (0.3)	6 (1.5)
Inability to resect the tumour	5 (1.3)	15 (3.8)
Death	50 (12.6)	40 (10.0)[e]

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

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

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[c] Based on Cox regression model with treatment as a covariate stratified by Stage (II vs III), TPS (>=50% vs <50%), Histology (squamous vs non-squamous) and Region (East-Asia vs non-East Asia), where Region is collapsed for Stage II TPS >=50% Non-squamous and Stage II TPS >=50% Squamous.

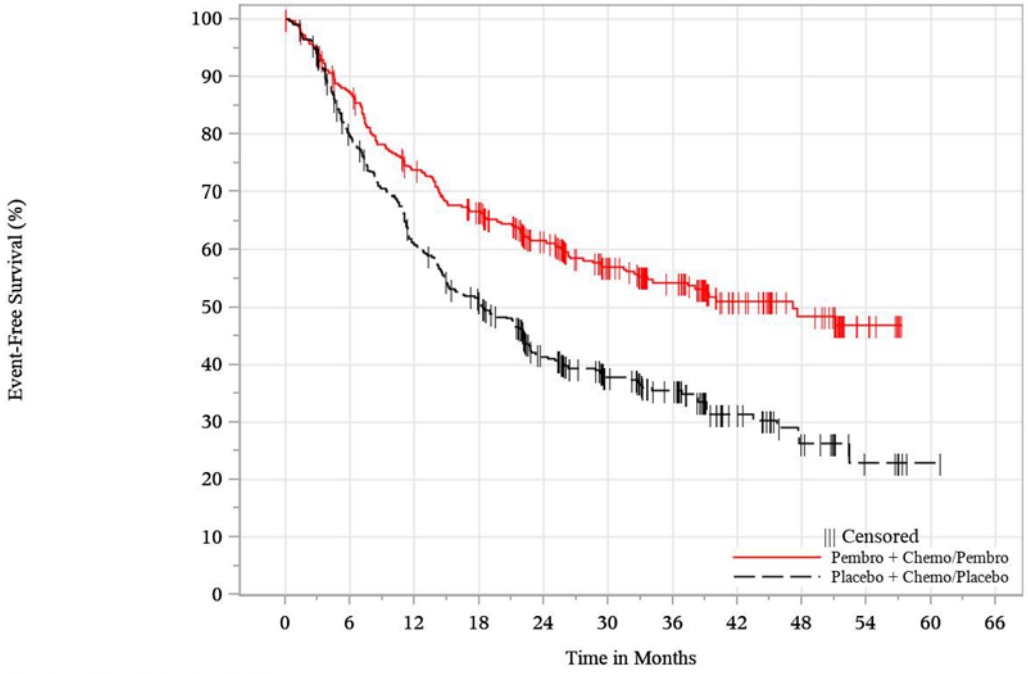
[d] One-sided p-value based on log-rank test stratified by Stage (II vs III), TPS (>=50% vs <50%), Histology (squamous vs non-squamous) and Region (East-Asia vs non-East Asia), where Region is collapsed for Stage II TPS >=50% Non-squamous and Stage II TPS >=50% Squamous.

[e] Although the number of deaths as a first event is higher in the pembrolizumab group, MSD note that the total number of deaths is fewer in the pembrolizumab arm compared with the placebo group (Table 17). The causes of death were predominantly malignant neoplasm progression, unknown causes, and Myocardial infarction rather than NSCLC.

Database cutoff date of 10 July 2023.

Abbreviations: CI, Confidence Interval; EFS, Event-free survival; HR, Hazard ratio; ITT, Intention to treat; NR, Not reached; TPS, Tumour proportion score.

Figure 7. Kaplan–Meier plot of event-free survival based on investigator assessment (ITT population)



Number of participants at risk

Pembro + Chemo/Pembro	397	339	282	250	196	142	102	62	37	10	0	0
Placebo + Chemo/Placebo	400	308	232	189	128	87	66	34	18	6	1	0

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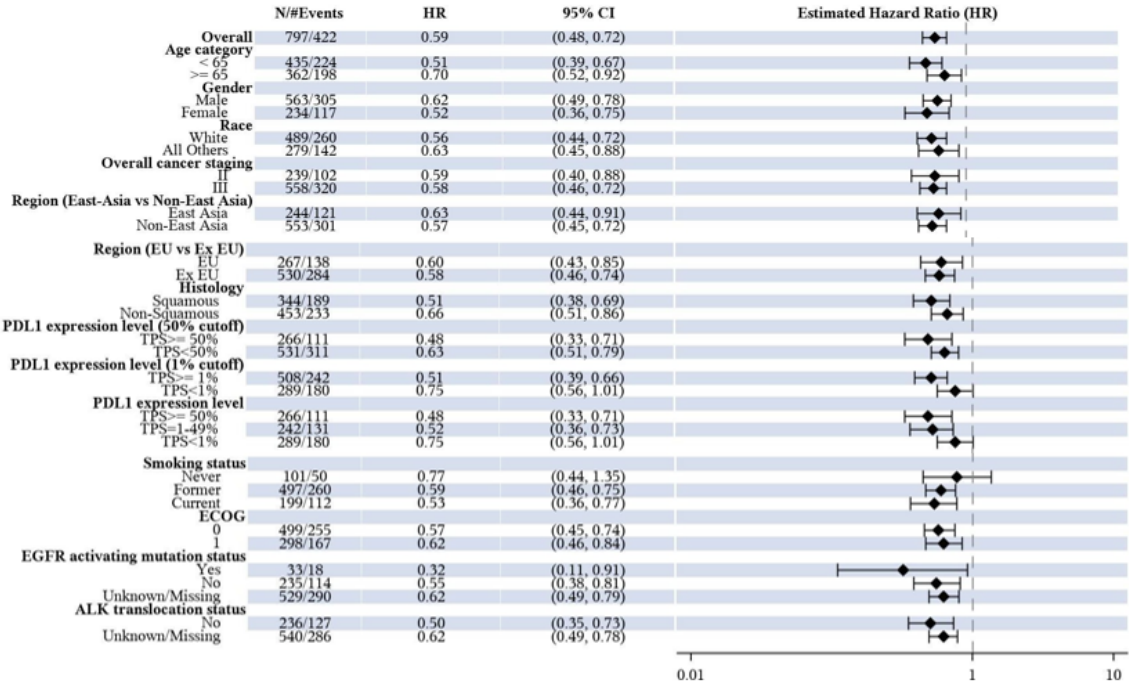
Figure 8. Forest plot of EFS hazard ratio by subgroup factors (primary censoring rule) based on investigator assessment (ITT population)



For overall population, analysis is based on stratified Cox regression model with treatment as a covariate. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
If a subgroup variable has two levels and one level of the subgroup has fewer than 30 participants, then this subgroup variable is not displayed in the plot. Database Cutoff Date: 10JUL2023

B.2.6.2.2. Overall survival

OS was formally tested at IA2 with the multiplicity-adjusted, one-sided p-value boundary of 0.005426. A statistically significant improvement in OS was observed with pembrolizumab compared with placebo (HR; 0.72; 95% CI: 0.56 to 0.93; p=0.00517), representing a 28% reduction in the risk of death (Table 17). Median OS was not reached in the pembrolizumab arm but was 52.4 months (95% CI: 45.7 to NR) in the placebo arm.

The KM plot for OS shows that the curve depicting events in the pembrolizumab arm separates from that of the placebo group at approximately Month 16 and remains separated over time (Figure 9). The OS benefit associated with pembrolizumab was generally consistent across the prespecified subgroups (Figure 10). Although the estimated HR for some analyses approaches 1, and for the East Asia subgroup was slightly above 1, it should be noted that OS data are immature, that the number of OS events in some subgroups is small and the CIs are wide, reflecting a level of uncertainty in the results and precluding drawing definitive conclusions on OS.

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Table 17. Analysis of overall survival (ITT population)

	Pembrolizumab[a] (N=397)	Placebo[a] (N=400)
Number of events, n (%)	110 (27.7)	144 (36.0)
Median OS, months (95% CI, months)[b]	NR (NR to NR)	52.4 (45.7 to NR)
OS HR (95% CI)[c]	0.72 (0.56 to 0.93)	
p-value[d]	0.00517	
OS rate at various time points (%) (95% CI)		
6 months	93.7 (90.8 to 95.7)	95.2 (92.6 to 96.9)
12 months	87.6 (84.0 to 90.5)	87.7 (84.0 to 90.5)
24 months	79.0 (74.6 to 82.7)	74.7 (70.1 to 78.7)
36 months	71.3 (66.2 to 75.8)	64.0 (58.5 to 68.9)
48 months	67.1 (61.1 to 72.3)	51.5 (43.9 to 58.6)

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

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

[c] Based on Cox regression model with treatment as a covariate stratified by Stage (II vs III), TPS (>=50% vs <50%), Histology (squamous vs non-squamous) and Region (East-Asia vs. non-East Asia), where Region and Histology are collapsed for Stage II TPS >=50%; Region is collapsed for Stage III TPS >=50% squamous and Stage II TPS <50% non-squamous.

[d] One-sided p-value based on log-rank test stratified by Stage (II vs III), TPS (>=50% vs <50%), Histology (squamous vs non-squamous) and Region (East-Asia vs non-East Asia), where Region and Histology are collapsed for Stage II TPS >=50%; Region is collapsed for Stage III TPS >=50% Squamous and Stage II TPS <50% non-squamous.

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Abbreviations: CI, Confidence Interval; HR, Hazard ratio; ITT, Intention to treat; NR, Not reached; OS, Overall survival; TPS, Tumour proportion score.

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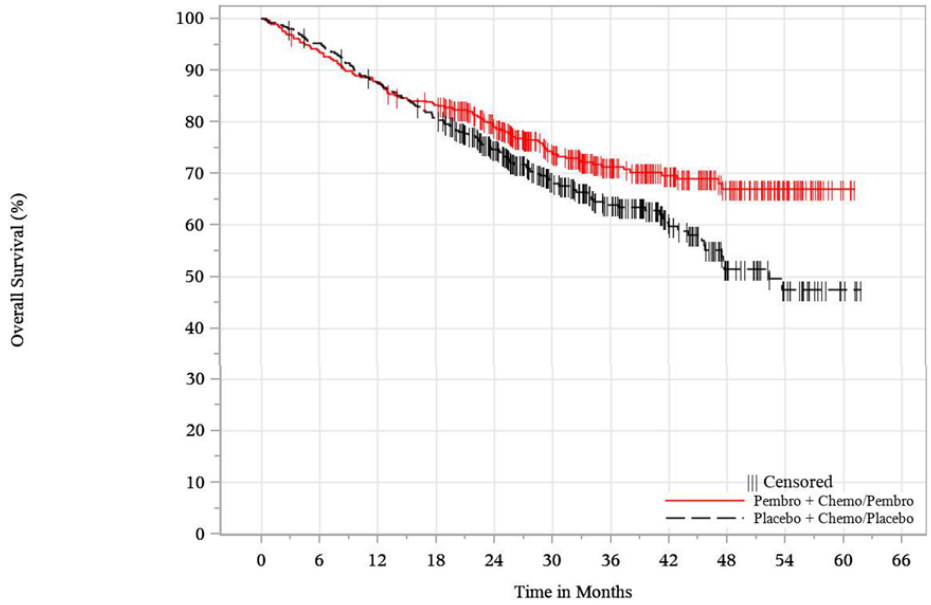
Figure 9. Kaplan–Meier plot of overall survival (ITT population)



Number of participants at risk

Pembro + Chemo/Pembro	397	371	347	327	277	205	148	108	69	32	4	0
Placebo + Chemo/Placebo	400	379	347	319	256	176	125	77	39	20	4	0

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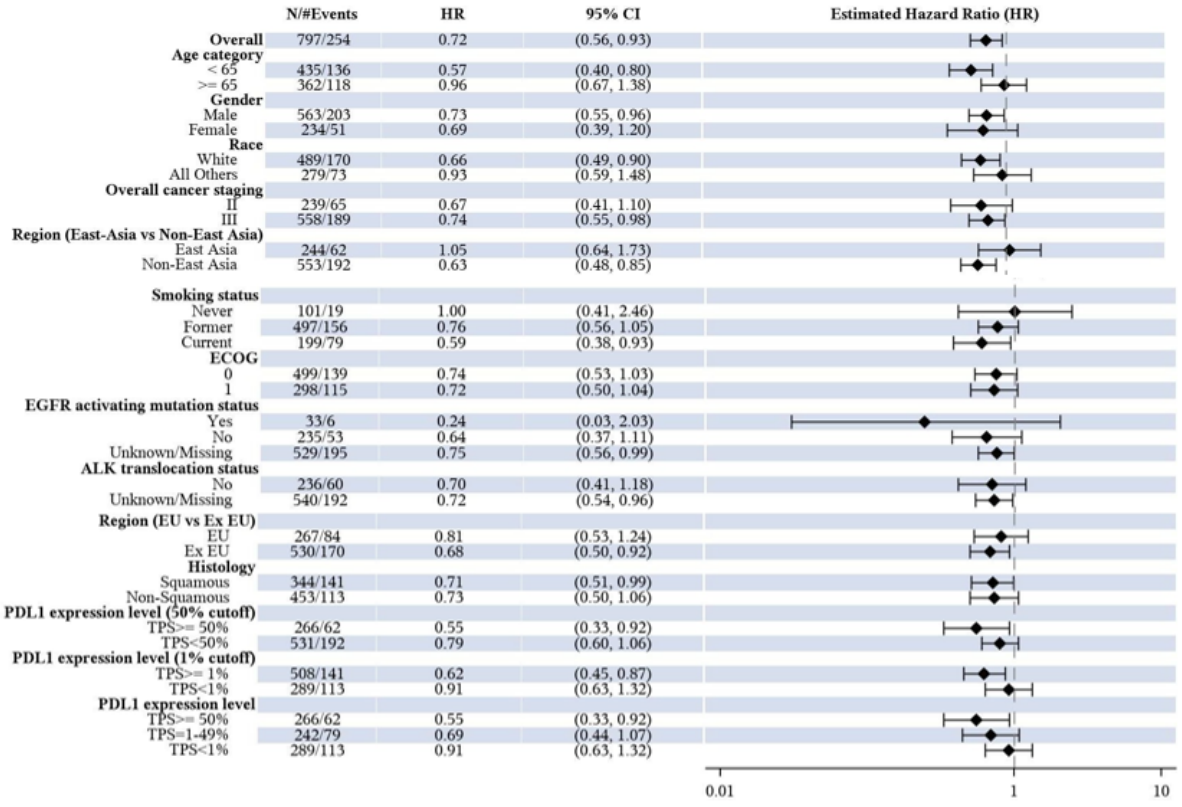
Figure 10. Forest plot of OS hazard ratio by subgroup factors (ITT population)



For overall population, analysis is based on stratified Cox regression model with treatment as a covariate. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
If a subgroup variable has two levels and one level of the subgroup has fewer than 30 participants, then this subgroup variable is not displayed in the plot. Database Cutoff Date: 10JUL2023

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B.2.6.3. Secondary outcomes

B.2.6.3.1. Pathological complete response

At IA1, KEYNOTE-671 met its key secondary objectives for pCR, with a statistically significant and clinically meaningful improvement in pCR based on blinded independent pathologist review (BIPR) in the pembrolizumab arm compared with the placebo arm (see Appendix E). Participants were scheduled to have had the opportunity for surgery by IA1 and so the pCR rate at IA2 was identical to that reported for IA1 and results for IA2 are descriptive. pCR was achieved by 18.1% of people allocated to pembrolizumab compared with 4.0% of those receiving placebo, with a difference in response rates of 14.2% (95% CI: 10.1 to 18.7; Table 18). The treatment differences for the pembrolizumab arm versus the placebo arm across all prespecified subgroups were consistent with the findings in the ITT population, and the pCR results by investigator assessment were consistent with those provided by BIPR (see Appendix E).

As discussed in Section B.1.3.1, clinical experts fed back to MSD that those patients who do not achieve pCR after surgery are the patients that they consider would likely gain the most benefit from continued treatment with pembrolizumab in the adjuvant setting, a strategy that is explored in a scenario in the cost-effectiveness analysis. Kaplan–Meier plots of EFS for those not achieving pCR show [redacted] for those treated with pembrolizumab and those in receipt of placebo (Figure 11).

Table 18. Analysis of pathological complete response based on BIPR assessment (ITT population)

Treatment	N	Number of patients achieving pCR	pCR rate (%) (95% CI)	Difference in %	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab[c]	397	72	18.1 (14.5 to 22.3)	14.2 (10.1 to 18.7)	<0.00001
Placebo[c]	400	16	4.0 (2.3 to 6.4)		

[a] Based on Miettinen & Nurminen method stratified by Stage (II vs.. III), TPS (>=50% vs <50%), Histology (squamous vs non-squamous) and Region (East-Asia vs non-East Asia).

[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % >0.

[c] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

Database cutoff date: 10 July 2023.

Abbreviations: BIPR, Blinded independent pathologist review; ITT, Intention to treat; pCR, Pathological complete response.

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Figure 11. Kaplan–Meier plot of investigator-assessed EFS for patients achieving and not pCR (based on BIPR assessment)

Abbreviations: BIPR, Blinded independent pathologist review; EFS, Event-free survival; pCR, Pathological complete response.

B.2.6.3.2. Major pathological response

At IA1, based on BIPR, there was a statistically significant and clinically meaningful improvement in mPR in the pembrolizumab arm compared with the placebo arm. As with pCR, participants were scheduled to have undergone surgery by IA1 and so the mPR rate at IA2 was identical to that reported for IA1, and, therefore, the mPR analysis at IA2 is descriptive. mPR was achieved by 30.2% of those in the pembrolizumab arm and 11.0% in the placebo arm, with a difference of 19.2% (95% CI: 13.9 to 24.7; Table 19).

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Table 19. Analysis of major pathological response based on BIPR assessment (ITT population)

Treatment	N	Number of patients achieving mPR	mPR Rate (%) (95% CI)	Difference in %	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab[c]	397	120	30.2 (25.7 to 35.0)	19.2 (13.9 to 24.7)	<0.00001
Placebo[c]	400	44	11.0 (8.1 to 14.5)		

[a] Based on Miettinen and Nurminen method stratified by Stage (II vs III), TPS (>=50% vs <50%), Histology (squamous vs non-squamous) and Region (East-Asia vs non-East Asia).

[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % >0.

[c] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

Database cutoff date 10 July 2023

Abbreviations: BIPR, Blinded independent pathologist review; ITT, Intention to treat; mPR, Major pathological response.

B.2.6.1. Patient reported outcomes

The baseline PRO assessment was that taken at neoadjuvant cycle 1. The mean change from baseline in the neoadjuvant treatment phase was evaluated at the neoadjuvant Week 11 PRO assessment. At the database cutoff date (10 July 2023) within the adjuvant treatment phase, Week 10 PRO assessment was selected as the primary timepoint for the mean change from baseline analysis to ensure that completion rates met approximately ≥60% and compliance rates met approximately ≥80% across the treatment groups.

B.2.6.1.1. EORTC QLQ-C30 Global Health Status/Quality of Life and supportive PRO analyses

The completion rate of the EORTC QLQ-C30 was above 90% at baseline and was the same in both groups (98.2%). Completion rates remained high at both Week 11 in the neoadjuvant phase (87.1% with pembrolizumab vs 88.9% with placebo) and at Week 10 in the adjuvant phase (68.6% with pembrolizumab vs 62.1% with placebo). Global health status/QoL scores decreased relative to baseline in both treatment groups in the neoadjuvant phase, showing deterioration in QoL. However, in the adjuvant phase, scores were stable relative to baseline. There was no statistically significant difference between pembrolizumab and placebo in change from baseline EORTC QLQ-C30 score in either the neoadjuvant or adjuvant phase:

- Neoadjuvant phase: difference in LS means of 1.43 (95% CI: –1.64 to 4.49; p=0.3611);
- Adjuvant phase: difference in LS means of 2.22 (95% CI: –0.58 to 5.02; p=0.1197).

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Detailed results are available in Appendix E.

B.2.6.1.2. EQ-5D

The completion rate of the EQ-5D-5L was above 90% at baseline and similar in both the pembrolizumab arm and placebo arm (98.5% vs 98.2%) and remained high at both Week 11 in the neoadjuvant phase (87.3% vs 89.2%) and at Week 10 in the adjuvant phase (68.6% vs 61.9%).

EQ-5D-5L VAS

In the neoadjuvant phase, the EQ-5D-5L visual analogue scale (VAS) scores [redacted] relative to baseline in both treatment groups at neoadjuvant Week 11, indicating a [redacted] in QoL. However, there was [redacted] between pembrolizumab and placebo in change in EQ-5D-5L VAS, with a difference in LS means of [redacted] (95% CI: [redacted]; Table 20). In the adjuvant phase, EQ-5D-5L VAS results were [redacted] in both the pembrolizumab and placebo arms at adjuvant Week 10, with [redacted] in score between the treatment arms (difference in LS means of [redacted]; Table 20).

Table 20. Analysis of change in EQ-5D-5L VAS from baseline for neoadjuvant and adjuvant phases (PRO FAS population)

	Baseline		Neoadjuvant Week 11		Change from baseline to Neoadjuvant week 11	
Neoadjuvant phase						
Treatment	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**LS mean (95% CI)[a]**
Pembrolizumab[b]	389	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo[b]	392	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise comparison: pembrolizumab vs placebo						
Difference in LS means[a] (95% CI)					[redacted]	
p-Value[a]					[redacted]	
	Baseline		**Adjuvant Week 10**		**Change from baseline to Adjuvant week 10**	
Adjuvant phase						
Treatment	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**LS mean (95% CI)[a]**
Pembrolizumab[b]	389	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo[b]	392	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Pairwise comparison: pembrolizumab vs placebo	
Difference in LS means[a] (95% CI)	[redacted]
p-Value[a]	[redacted]

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by visit interaction and stratification factors (Stage (II vs III), TPS (>=50% vs <50%), Histology (squamous vs non-squamous) and Region (East-Asia vs. non-East Asia). P-value is based on two-sided t test.

[b] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

For baseline and Neoadjuvant Week 11, 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 of 10 July 2023.

Abbreviations: CI, Confidence interval; FAS, Full analysis set; LS, Least squares; PRO, Patient reported outcome; SD, Standard deviation; VAS, Visual analogue scale.

B.2.7. Meta-analysis

Only one head-to-head study evaluating pembrolizumab in the setting relevant to this technology appraisal was identified (KEYNOTE-671) and, thus, meta-analysis was not possible. Estimates of comparative clinical effectiveness for pembrolizumab versus comparators of interest as set out in the decision problem (Table 1) were derived from a network meta-analysis (NMA), the results of which are presented in section B.2.8.

B.2.8. Indirect and mixed treatment comparisons

An SLR was carried out as per NICE guidance and according to a pre-specified protocol to identify and select relevant evidence on the efficacy of pembrolizumab and treatments administered either neoadjuvantly or peri-adjuvantly. Studies evaluating treatments in the adjuvant setting were not eligible for inclusion. MSD note that the SLR was carried out for a broader research project than that set out in the final scope issued by NICE.(2) The list of included studies was re-reviewed to identify those trials evaluating the intervention and comparators listed in the NICE scope. The NMA was carried out in line with guidance from NICE Decision Support Unit on methods for evidence synthesis.(50-53) Full details of the SLR and NMA methodologies are available in Appendix D.

Below, MSD present results for only EFS. As discussed in Section 1.3.1, in early-stage NSCLC, patients are typically at higher risk of recurrence than death, and so EFS is potentially a more clinically relevant outcome than OS for this stage of disease:

- EFS was the primary outcome in CheckMate-816 and a co-primary outcome in KEYNOTE-671;

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- The most frequently occurring first event of EFS in KEYNOTE-671 in both arms was progression/recurrence, with 68% and 75% of all reported EFS events to date attributed to progression/recurrence in the pembrolizumab and placebo groups, respectively (Table 16);
- OS data from the identified RCTs are immature and so definitive conclusions on treatment effect on OS cannot be drawn from the direct comparisons, and, consequently, not from indirect comparisons of clinical effectiveness derived from a network informed by the immature direct evidence;
- OS is not included in MSD's analysis of cost effectiveness.

B.2.8.1. Indirect treatment comparison for the outcome of EFS

B.2.8.1.1. Summary of the trials included in the network

The SLR identified five RCTs(20, 45, 54-56) that met the prespecified eligibility criteria and together facilitated the generation of a network for EFS evaluating four interventions of interest to the decision problem (Table 1; Figure 12):

- Neoadjuvant pembrolizumab plus chemotherapy and then adjuvant pembrolizumab monotherapy;
- Neoadjuvant nivolumab with chemotherapy;
- Platinum-based chemotherapy (neoadjuvant);
- Active monitoring (i.e., surgery alone).

As discussed earlier, MSD do not consider neoadjuvant chemoradiotherapy to be a relevant comparator for the population that is the focus of this technology appraisal.

Assumptions made to enable creation of the network are:

- Cisplatin plus gemcitabine and cisplatin plus pemetrexed are of similar clinical efficacy;
- Treatments pooled within each node are of similar clinical efficacy;
- No adjuvant therapy in the study is equivalent to receiving placebo in the adjuvant setting;
- EFS, PFS, and DFS outcomes have been considered to measure similar events.

Of the five included RCTs, three studies evaluated neoadjuvant chemotherapy versus surgery alone, all of which were over 10 years old, with results published between 2009 and 2012.(54-56) It is these three studies that facilitate the creation of a network that allows

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indirect comparison of pembrolizumab with surgery alone and with neoadjuvant nivolumab plus chemotherapy (Figure 12). All three studies assessing neoadjuvant chemotherapy were terminated early due to the reporting of positive results from studies evaluating adjuvant chemotherapy.(54-56) Additionally, two of the studies do not report what system was used to stage NSCLC at study entry and so it is likely that there is variation across the studies in staging criteria (Table 21). The studies were all deemed to have some concerns about the risk of bias (Table 21). The categorisations of risk of bias reflect the methodological limitations associated with the early termination of the studies and the lack of detail available in the publications on key aspects of trial design, including methods of randomisation and the level of blinding within the study. Despite the identified concerns with the three trials, MSD consider that the studies represent the best available evidence to generate a network and enable comparison of pembrolizumab with neoadjuvant nivolumab plus chemotherapy and surgery alone.

The two remaining RCTs informing the network are those evaluating clinical effectiveness of pembrolizumab in the peri-adjuvant setting (KEYNOTE-671(20)) and of neoadjuvant nivolumab plus chemotherapy (CheckMate-816(45)). KEYNOTE-671 is a large (N=797), well-designed and well-conducted study deemed to be at an overall low risk of bias (Table 13 and Table 21). CheckMate 816 is a moderately sized (N=358), well-conducted study deemed to have some concerns around risk of bias, predominantly due to the open-label nature of the trial, which potentially introduces an element of bias in the assessment of EFS (discussed in more detail in Section 2.8.2).

For interpretation of the potential clinical sources of and direction of bias in the NMA, key baseline characteristics are considered to be age, and performance status, in addition to the stratification factors for randomisation in KEYNOTE-671 (stage, histology, TPS, and region). Age of participants was consistent across the five studies, with median age of 64 years or similar (Table 21). Baseline performance scores were also generally similar across the studies, but one study(55) had a smaller proportion of patients with a score of 0 at baseline, suggesting a less fit patient population compared with the other trials.

Differences across the studies were noted in proportion of participants with squamous NSCLC, the staging system, if any, implemented to stage NSCLC at baseline, and the location of the sites of the studies (Table 21). The potential impact of the identified sources of clinical heterogeneity on the extent and direction of bias introduced into the NMA are discussed in more detail in Section 2.8.2.

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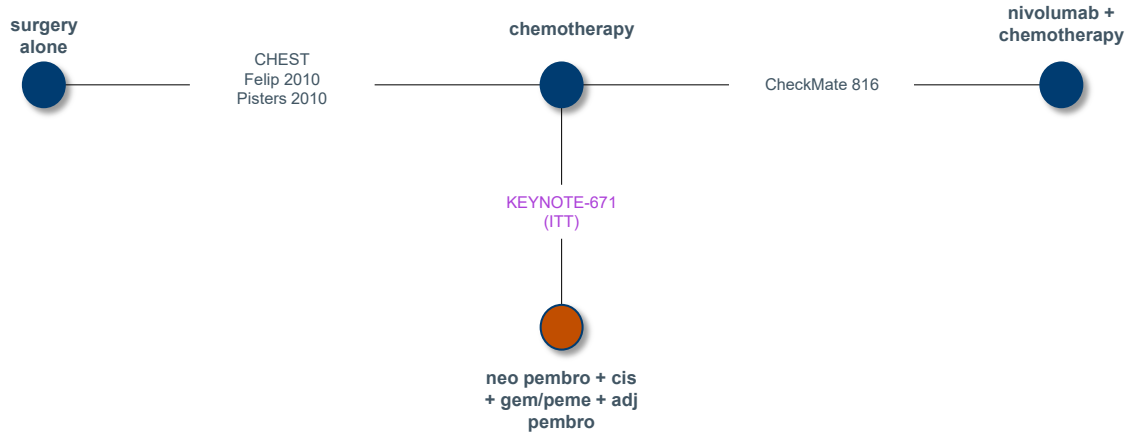
For the two studies evaluating immunotherapy, KEYNOTE-671 and CheckMate 816, the proportion of people having surgery was similar, with ~80% of randomised patients in both studies undergoing surgery (Table 21). In CheckMate 816, participants could receive up to 4 cycles of chemotherapy after surgery, with 11.9% and 22.2% of those in the neoadjuvant nivolumab plus chemotherapy and the chemotherapy-alone group, respectively, receiving adjuvant chemotherapy.

Figure 12. Network diagram for the outcome of EFS



References for included studies: CHEST;(54) Felip 2010;(55) Pisters 2010;(56) CheckMate 816;(45) KEYNOTE-671.(20, 46, 47)

Abbreviations: EFS, Event-free survival; ITT, Intention to treat.

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Table 21. Summary of key characteristics of the clinical studies informing the network for EFS

Characteristic	Trial				
	CHEST(54)	**Felip 2010(55)**	**Pisters 2010(56)**	**CheckMate 816(45)**	**KEYNOTE-671(20, 46, 47)**
N	270[a]	624	354[c]	358	797
Population	NSCLC stages I (except for T1N0), II, or IIIA (T3N1; excluding superior sulcus)[a]	NSCLC stages IA with tumor size >2 cm, IB, II, or T3N1[b]	NSCLC stages IA–IIIB[c]	NSCLC stage IB (≥4 cm) to IIIA[d]	NSCLC stage II or IIIA/B (T3-4N2)[e]
Intervention	Neoadjuvant gemcitabine plus cisplatin (3 cycles)	Arm 1: Neoadjuvant paclitaxel plus carboplatin (3 cycles) Arm 2: Adjuvant paclitaxel plus carboplatin (3 cycles)	Neoadjuvant paclitaxel plus carboplatin (3 cycles)	Neoadjuvant nivolumab plus platinum-doublet chemotherapy (3 cycles)	Neoadjuvant pembrolizumab plus cisplatin-based-doublet chemotherapy (4 cycles) followed by surgery and then adjuvant pembrolizumab (13 cycles)
Comparator	Surgery alone	Surgery alone	Surgery alone	Neoadjuvant platinum-doublet chemotherapy (3 cycles)	Neoadjuvant cisplatin-based - doublet chemotherapy (4 cycles)
Key baseline characteristics					
Age, years	Median: 61.8	Median: 64	Median: 64 in intervention group Median: 65 in comparator group	Median: 64 in intervention group Median: 65 in comparator group	Median: 64
Performance score	0: 72% 1: 28%	0: 46% 1: 52.4%	0: 65% 1: 35%	0: 67% 1: 33%	0: 63% 1: 37%

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Stage (II, III)	IB/IIA: 52% IIB/IIIA: 48%	Unclear	IB/IIA: 68% IIB/IIIA: 32%	IB or II: 35.4% IIIA: 64.6%	II: 30% IIIA: 55% IIIB: 14%
TPS (<50%, ≥50%)	N/R	N/R	N/R	<50%: 70.6% ≥50%: 22.4%	<50%: 66.6% ≥50%: 33.4%
Histology (squamous, non-squamous)	Squamous: 41% Non-squamous: 59%	Squamous: 51% Non-squamous: 49%	Squamous: 38% Non-squamous: 62%	Squamous: 51% Non-squamous: 49%	Squamous: 43% Non-squamous: 57%
Region (East Asia, non-East Asia)	N/R by region: 99% of patients enrolled were White.	N/R Ethnicity not reported in baseline characteristics	N/R Ethnicity not reported in baseline characteristics	Asia: 49.5% Rest of world: 50.5%	East Asia: 30.6% Non-East Asia: 69.4%
Follow-up	Median: 3.3 years for chemo plus surgery vs 2.6 years for surgery	Median: 51 months	Median: 64 months	Median: 29.5 months	Median: 29.8 months
Outcome, HR (95% CI); p value	PFS 0.70 (0.50 to 0.97); p=0.03	DFS for neoadjuvant chemotherapy vs surgery 0.92 (0.81 to 1.04); p=0.17	PFS 0.80 (0.61 to 1.04); p=0.10)	EFS (BICR)(45) Unadjusted 0.63 (97.38% CI: 0.43 to 0.91); p=0.005 Adjusted for adjuvant therapy 0.65 (0.47 to 0.90) EFS at 3 years: 0.68 (0.49 to 0.93)(57)	EFS (IA) 0.59 (0.48 to 0.72); p<0.00001
Overall risk of bias	Some concerns	Some concerns	Some concerns	Some concerns	Low

[a] Based on 5th Edition of the AJCC. Study terminated early because of reporting of positive results from trial evaluating adjuvant chemotherapy.

[b] Baseline clinical stage is reported in terms of T, N and M rather than overall stage and it is unclear what system has been used to stage the tumours. It is reported that 75.1% of patients had clinical stage I disease and 23.8% of patients who underwent surgery had stage IIIA/N2 at the time of surgery.

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[c] Unclear which tool was used to stage tumours. Study was terminated early after reports of an OS benefit from postoperative chemotherapy in patients with resected NSCLC.

[d] Based on 7th Edition of the AJCC. Patients with known ALK translocations or EGFR mutations were excluded. After surgery, patients in both groups could receive up to 4 cycles of adjuvant chemotherapy, radiotherapy, or both. Adjuvant chemotherapy was received by 11.9% of the patients in the nivolumab-plus-chemotherapy group and 22.2% of those in the chemotherapy-alone group. Of patients who underwent concurrent randomization, 83.2% in the nivolumab plus-chemotherapy group and 75.4% in the chemotherapy-alone group underwent definitive surgery.

[e] Based on the 8th edition of the AJCC. If a participant did not undergo surgery due to refusal, physician decision, medical illness, or any reason other than local progression or metastatic disease, they were to receive radiotherapy and continue to the adjuvant phase. After surgery, those with microscopic residual disease or gross residual disease in the tumour bed could undergo radiotherapy. In the pembrolizumab group, 396 participants received at least one dose of neoadjuvant pembrolizumab plus chemotherapy and 325 (82.1%) underwent in-trial surgery, with 290 (73.2%) receiving at least one dose of adjuvant pembrolizumab. In the placebo group, 399 participants received at least one dose of neoadjuvant placebo plus chemotherapy and 317 (79.4%) underwent in-trial surgery, with 267 (66.9%) receiving at least one dose of adjuvant placebo.

Abbreviations: AJCC, American Joint Committee on Cancer; ALK, Anaplastic lymphoma kinase; BICR, Blinded independent central review; CI, Confidence interval; DFS, Disease-free survival; ECOG, Eastern Cooperative Oncology Group; EGFR, Epidermal growth factor receptor; HR, Hazard ratio; IA, Investigator assessed; N/R, Not reported; NSCLC, Non-small cell lung cancer; OS, Overall survival; PFS, Progression-free survival; Vs, versus.

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B.2.8.1.2. Estimates of comparative clinical effectiveness for EFS

Fixed and random effects NMAs with both time-constant and time-varying HRs for EFS were carried out. An overview of the results from time constant and time-varying HR NMAs based on investigator-assessed EFS from KEYNOTE-671 is presented in Table 22. Results from MSD's preferred analysis are highlighted in bold in Table 22, and these results inform MSD's base case in the analysis of cost effectiveness. More detailed descriptions of the rationale underlying MSD's choice of set of NMA results, together with additional results and the limitations of the NMAs are available in the sections that follow and in Appendix D.

Table 22. Summary of EFS for time constant and time-varying NMAs

Analysis	HR (95% CrI)	
	Peri-adjuvant pembrolizumab versus surgery alone	*Peri-adjuvant pembrolizumab versus neoadjuvant nivolumab*
Time-varying		
Fixed effects	**3 months: 0.49 (0.33 to 0.71)** **12 months: 0.48 (0.37 to 0.63)** **48 months: 0.48 (0.32 to 0.70)**	**3 months 1.30 (0.72 to 2.36)** **12 months: 0.79 (0.53 to 1.18)** **48 months: 0.61 (0.34 to 1.10)**
Random effects	3 months: 0.47 (0.14 to 1.39) 12 months: 0.48 (0.14 to 1.37) 48 months: 0.48 (0.14 to 1.38)	3 months: 1.26 (0.31 to 4.60) 12 months: 0.79 (0.20 to 2.70) 48 months: 0.62 (0.15 to 2.19)
Time constant		
Fixed effects	0.52 (0.41 to 0.65)	0.87 (0.59 to 1.27)
Random effects	0.49 (0.09 to 2.56)	0.87 (0.10 to 7.27)

Abbreviations: CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis.

<u>MSD's rationale for carrying out both time-constant and time-varying HR NMAs</u>

The HRs informing the time-constant NMAs were obtained from the published literature, and, therefore, are derived from aggregate level survival data and rely on the assumption of proportional hazards, which is not the case for analyses based on a time-varying approach. The proportional hazards assumption is violated when the relationship of the hazard functions is not constant between the treatment arms in the study, for example, the survival curves are trending towards intersecting or diverging, which means that the HR is not constant.

Standard statistical tests to determine whether proportional hazards had been violated in EFS for the studies informing the network indicated that the assumption of proportional hazards held, that is, the null hypothesis of constant between study HR over time could not be rejected. However, MSD note that the standard tests used to evaluate the assumption are underpowered to detect all but the most pronounced violations of proportional hazards.(58) Some authors have suggested that a null hypothesis of non-proportional hazards would be a

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more biologically plausible basis for statistical tests.(59) MSD also note that it is now standard in oncology submissions to NICE for within-trial curves to be modelled independently with implicitly non-proportional hazards. MSD considers it logical that the same considerations regarding hazard function over time would apply to an indirect comparator as to a direct one.

Analyses based on fractional polynomials have the benefit that they can capture a non-constant relationship between the hazard functions of the various interventions in the network over time, which is especially useful for networks including treatments with different mechanisms of action and that are given for different durations, as is the case for the network of EFS presented below. Therefore, fixed and random effects NMAs of EFS with time-varying HRs using fractional polynomials were carried out in addition to the NMA using constant HRs.

MSD's preferred NMA

The course of hazards over time was investigated for the two immunotherapy trials, KEYNOTE-671 and CheckMate 816, as depicted in Figure 13 (see appendix D.3 for further details). MSD note that [redacted].

MSD considers that it is biologically plausible that trends in hazard ratios would vary over time for the following reasons,

- Surgery occurs at different timepoints for each comparator (0 weeks for surgery alone, 11 weeks for nivolumab, 15 weeks for pembrolizumab) – it lacks face validity for hazard ratios to be constant given different timings of surgical intervention;
- Pembrolizumab has been demonstrated to be clinically effective in the adjuvant setting in the KEYNOTE-091 trial.(60) The initiation of pembrolizumab after surgery in the adjuvant setting would be expected to impact the hazard ratio versus the other comparators by having the potential to eliminate any distant micro-metastases that might remain after surgery (see section B.1.3.2).

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Given [redacted] the biological rationale outlined above, MSD consider the results for the estimates of comparative clinical effectiveness derived from time-varying HR NMAs to be the more appropriate to inform decision making.

Figure 13. EFS HR (95% CI) versus chemotherapy over time in CheckMate-816 and KEYNOTE-671 based on best-fitting fractional polynomials model using the Gompertz distribution

Considering random and fixed effects models, MSD present the results from both models, and indicate which model statistical analyses indicated to be the best fit to the data. MSD note that tests assessing model fit indicated no meaningful difference between random and fixed effects models in either time-constant or time-varying HRs. The fixed-effect model assumes that there is one true effect size that underlies each of the comparisons in the network, and that all differences in the observed effect sizes are due to sampling error.(61) By contrast, the random effects model is based on the inherent assumption that the true effect could vary from study to study because of heterogeneity across studies, which is reflected in the wider CIs or CrIs generated by the analysis.(61) Given that KEYNOTE-671 is a large (N=797), well-designed and well-conducted study, MSD consider that the true effect

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size of pembrolizumab versus neoadjuvant chemotherapy (equivalent to the placebo arm in KEYNOTE-671) is captured in the reported HR and 95%CI for the study, and, thus, the results from the fixed effect models are the most appropriate for decision-making. Additionally, in the network of the EFS (Figure 12), it is noted that the link involving CheckMate 816 is also informed by a single RCT and, therefore, MSD consider it logical that the indirect comparison between the two immunotherapy interventions is better informed by the fixed effects model rather than importing statistical heterogeneity from the chemotherapy versus surgery component of the network.

Results from time-varying HR NMAs

The best fitting curves in the Weibull and Gompertz families were plausible options to select to inform the time-varying HR. The Weibull curve (P1=0, P2=-0.5 and 2nd shape) was chosen based on having the lowest DIC among any model, having good visual fit to the data and having plausible hazard ratios over time. Of note, in the Weibull model, the HR between peri-adjuvant pembrolizumab and neoadjuvant nivolumab is closer to that observed in the initial analysis (Figure 13) without the neoadjuvant chemotherapy versus surgery alone studies. This suggests less bias has been introduced to the indirect comparison of the immunotherapy studies by the inclusion of these other studies in the network than in the Gompertz model, where the neo-adjuvant chemotherapy versus surgery comparison appears to have more influence. As would be expected, CrIs are wider with the random effects model.

For investigator-assessed EFS, fixed-effect, time-varying HR NMA showed peri-adjuvant pembrolizumab to be statistically significantly more effective than neoadjuvant chemotherapy at improving EFS at each time point evaluated (Table 23). Results from the random effects, time-varying HR NMA generated similar effect sizes as the fixed effects analysis, but with wider CrIs, and no difference reached statistical significance (Table 24). Selected time points for fixed effect analysis of EFS for peri-adjuvant pembrolizumab versus neoadjuvant chemotherapy are:

- 3 months: HR 0.72 (95% CrI: 0.52 to 0.97);
- 12 months: HR 0.55 (95% CI: 0.45 to 0.68);
- 24 months: HR 0.51 (95% CI: 0.40 to 0.66);
- 36 months; HR 0.50 (95% CI: 0.37 to 0.66).

Fixed effect, time-varying HR NMA indicated that peri-adjuvant pembrolizumab was associated with statistically significant improvement in investigator-assessed EFS at all time

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points (Table 25), but there was no difference in effect between peri-adjuvant pembrolizumab and neoadjuvant nivolumab, although the direction of effect favoured peri-adjuvant pembrolizumab at most time points (Table 26). Selected time points for fixed effect analysis of EFS for peri-adjuvant pembrolizumab versus neoadjuvant chemotherapy are:

- 3 months:
    - Surgery alone: HR 0.49 (95% CrI: 0.33 to 0.71);
    - Neoadjuvant nivolumab: HR 1.30 (95% CrI: 0.72 to 2.36);
- 12 months:
    - Surgery alone: HR 0.48 (95% CrI: 0.37 to 0.63);
    - Neoadjuvant nivolumab: HR 0.79 (95% CrI: 0.53 to 1.18);
- 24 months: HR 0.51 (95% CI: 0.40 to 0.66);
    - Surgery alone: HR 0.48 (95% CrI: 0.34 to 0.66);
    - Neoadjuvant nivolumab: HR 0.68 (95% CrI: 0.42 to 1.12);
- 36 months; HR 0.50 (95% CI: 0.37 to 0.66):
    - Surgery alone: HR 0.48 (95% CrI: 0.33 to 0.68);
    - Neoadjuvant nivolumab: HR 0.64 (95% CrI: 0.37 to 1.10).

The curves from the Weibull fixed effects model are shown in Figure 14. Results from the Weibull random effects model, and the best-fitting Gompertz family curves, are presented in Appendix D.

Results from constant and time-varying HR NMAs implementing BICR assessment of EFS for KEYNOTE-671 produced similar estimates of effect to the primary analyses. Results from all NMAs of EFS along with model diagnostics are presented in Appendix D.

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Table 23. Summary of results from NMA with time-varying HR of treatments for the outcome of EFS versus chemotherapy: Weibull (P1=0 P2=-0.5, scale, 2nd shape), fixed effects method

Comparator versus chemotherapy	Time-varying HR (95% CrI)											
	Time in months											
	3	6	9	12	18	24	30	36	42	48	54	60
Surgery alone	**1.47 (1.17, 1.87)**	**1.28 (1.08, 1.51)**	**1.20 (1.02, 1.41)**	1.15 (0.97, 1.37)	1.10 (0.91, 1.33)	1.07 (0.88, 1.31)	1.05 (0.85, 1.30)	1.04 (0.84, 1.29)	1.03 (0.82, 1.29)	1.02 (0.81, 1.28)	1.01 (0.80, 1.28)	1.00 (0.79, 1.28)
Neoadjuvant nivolumab	**0.55 (0.33, 0.90)**	**0.63 (0.45, 0.88)**	**0.67 (0.49, 0.93)**	**0.70 (0.50, 0.99)**	0.73 (0.50, 1.08)	0.75 (0.50, 1.14)	0.77 (0.49, 1.19)	0.78 (0.49, 1.23)	0.79 (0.49, 1.27)	0.79 (0.49, 1.29)	0.80 (0.48, 1.32)	0.80 (0.48, 1.34)
Peri-adjuvant pembrolizumab	**0.72 (0.52, 0.97)**	**0.62 (0.50, 0.75)**	**0.58 (0.47, 0.70)**	**0.55 (0.45, 0.68)**	**0.53 (0.42, 0.66)**	**0.51 (0.40, 0.66)**	**0.50 (0.38, 0.66)**	**0.50 (0.37, 0.66)**	**0.49 (0.36, 0.66)**	**0.49 (0.36, 0.66)**	**0.48 (0.35, 0.66)**	**0.48 (0.35, 0.66)**

Note: HRs represent the effect estimate for the comparator versus chemotherapy (i.e., HR <1 favours comparator, HR >1 favours chemotherapy). Cells shaded in grey indicate estimates based on model extrapolations. All **bolded** values are statistically significant at the 0.05 significance level.

Abbreviations: CrI, Credible interval; DIC, Deviance information criterion; EFS, Event-free survival; NMA, Network meta-analysis.

Table 24. Summary of results from NMA with time-varying HR of treatments for the outcome of EFS versus chemotherapy: Weibull (P1=0 P2=-0.5, scale, 2nd shape, random effects method

Comparator	Time-varying HR (95% CrI)											
	Time in months											
	3	6	9	12	18	24	30	36	42	48	54	60
Surgery alone	1.49 (0.85, 2.68)	1.28 (0.74, 2.32)	1.20 (0.69, 2.17)	1.16 (0.66, 2.09)	1.11 (0.63, 2.00)	1.08 (0.61, 1.95)	1.06 (0.60, 1.93)	1.04 (0.59, 1.91)	1.03 (0.58, 1.89)	1.02 (0.58, 1.87)	1.02 (0.57, 1.86)	1.01 (0.57, 1.85)
Neoadjuvant nivolumab	0.56 (0.21, 1.59)	0.64 (0.25, 1.75)	0.68 (0.26, 1.85)	0.70 (0.27, 1.92)	0.73 (0.28, 2.03)	0.75 (0.28, 2.11)	0.76 (0.29, 2.15)	0.77 (0.29, 2.19)	0.78 (0.29, 2.22)	0.79 (0.29, 2.26)	0.79 (0.29, 2.28)	0.80 (0.29, 2.31)
Peri-adjuvant pembrolizumab	0.70 (0.27, 1.76)	0.61 (0.23, 1.49)	0.57 (0.22, 1.39)	0.55 (0.21, 1.34)	0.53 (0.20, 1.29)	0.51 (0.19, 1.26)	0.51 (0.19, 1.23)	0.50 (0.19, 1.22)	0.49 (0.18, 1.21)	0.49 (0.18, 1.20)	0.49 (0.18, 1.20)	0.48 (0.18, 1.19)

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Note: HRs represent the effect estimate for the comparator versus chemotherapy (i.e., HR <1 favours comparator, HR >1 favours chemotherapy). Cells shaded in grey indicate estimates based on model extrapolations.

Abbreviations: CrI, Credible interval; DIC, Deviance information criterion; EFS, Event-free survival; NMA, Network meta-analysis.

Table 25. Summary of results from NMA with time-varying HR of treatments for the outcome of EFS of peri-adjuvant pembrolizumab versus relevant comparators: Weibull (P1=0 P2=-0.5, scale, 2nd shape), fixed effects method

Comparator	Time-varying HR (95% CrI)											
	Time in months											
	3	6	9	12	18	24	30	36	42	48	54	60
Neoadjuvant chemotherapy	**0.72 (0.52, 0.97)**	**0.62 (0.50, 0.75)**	**0.58 (0.47, 0.70)**	**0.55 (0.45, 0.68)**	**0.53 (0.42, 0.66)**	**0.51 (0.40, 0.66)**	**0.50 (0.38, 0.66)**	**0.50 (0.37, 0.66)**	**0.49 (0.36, 0.66)**	**0.49 (0.36, 0.66)**	**0.48 (0.35, 0.66)**	**0.48 (0.35, 0.66)**
Surgery alone	**0.49 (0.33, 0.71)**	**0.48 (0.37, 0.62)**	**0.48 (0.37, 0.62)**	**0.48 (0.37, 0.63)**	**0.48 (0.35, 0.65)**	**0.48 (0.34, 0.66)**	**0.48 (0.34, 0.67)**	**0.48 (0.33, 0.68)**	**0.48 (0.33, 0.69)**	**0.48 (0.32, 0.70)**	**0.48 (0.32, 0.71)**	**0.48 (0.32, 0.71)**
Neoadjuvant nivolumab	1.30 (0.72, 2.36)	0.97 (0.66, 1.43)	0.85 (0.58, 1.24)	0.79 (0.53, 1.18)	0.72 (0.46, 1.13)	0.68 (0.42, 1.12)	0.66 (0.39, 1.11)	0.64 (0.37, 1.10)	0.63 (0.36, 1.10)	0.61 (0.34, 1.10)	0.61 (0.33, 1.10)	0.60 (0.33, 1.10)

Note: HRs represent the effect estimate for peri-adjuvant pembrolizumab versus the comparator (i.e., HR <1 favours peri-adjuvant pembrolizumab, HR >1 favours comparator). Cells shaded in grey indicate estimates based on model extrapolations. All **bolded** values are statistically significant at the 0.05 significance level.

Abbreviations: CrI, Credible interval; DIC, Deviance information criterion; EFS, Event-free survival; NMA, Network meta-analysis.

Table 26. Summary of results from NMA with time-varying HR of treatments for the outcome of EFS of peri-adjuvant pembrolizumab versus relevant comparators: Weibull (P1=0 P2=-0.5, scale, 2nd shape), random effects method

Comparator	Time-varying HR (95% CrI)											
	Time in months											
	3	6	9	12	18	24	30	36	42	48	54	60
Neoadjuvant chemotherapy	0.70 (0.27, 1.76)	0.61 (0.23, 1.49)	0.57 (0.22, 1.39)	0.55 (0.21, 1.34)	0.53 (0.20, 1.29)	0.51 (0.19, 1.26)	0.51 (0.19, 1.23)	0.50 (0.19, 1.22)	0.49 (0.18, 1.21)	0.49 (0.18, 1.20)	0.49 (0.18, 1.20)	0.48 (0.18, 1.19)

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Surgery alone	0.47 (0.14, 1.39)	0.47 (0.14, 1.36)	0.48 (0.14, 1.36)	0.48 (0.14, 1.37)	0.48 (0.14, 1.37)	0.48 (0.14, 1.36)	0.48 (0.14, 1.37)	0.48 (0.14, 1.37)	0.48 (0.14, 1.38)	0.48 (0.14, 1.38)	0.48 (0.14, 1.39)	0.48 (0.14, 1.39)
Neoadjuvant nivolumab	1.26 (0.31, 4.60)	0.96 (0.24, 3.27)	0.85 (0.21, 2.90)	0.79 (0.20, 2.70)	0.72 (0.18, 2.48)	0.68 (0.17, 2.35)	0.66 (0.16, 2.28)	0.64 (0.15, 2.25)	0.63 (0.15, 2.21)	0.62 (0.15, 2.19)	0.61 (0.14, 2.17)	0.61 (0.14, 2.15)
Note: HRs represent the effect estimate for peri-adjuvant pembrolizumab versus the comparator (i.e., HR <1 favours peri-adjuvant pembrolizumab, HR >1 favours comparator). Cells shaded in grey indicate estimates based on model extrapolations.												

Abbreviations: CrI, Credible interval; DIC, Deviance information criterion; EFS, Event-free survival; NMA, Network meta-analysis.

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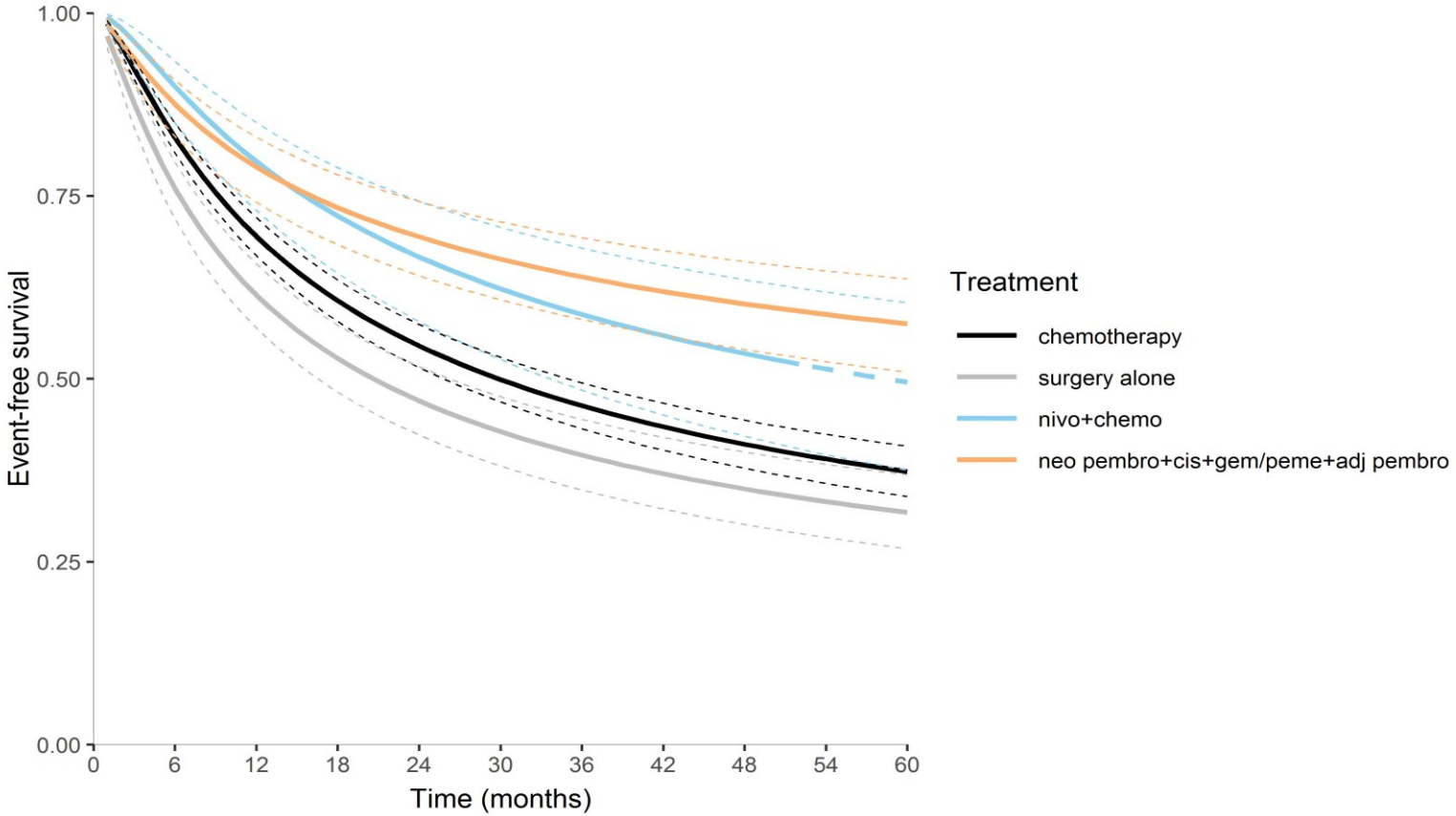
Figure 14. EFS curves from NMA with time-varying HR: Weibull (P1=0 P2=-0.5, scale, 2nd shape), fixed effects method



Dotted lines represent 95% CrIs.

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Results from time constant HR NMAs

The DIC and deviation at the posterior mean of the model within each network showed the fixed effects NMA to be the better fitting model. The NMA indicates that pembrolizumab is associated with statistically significant improvements in EFS compared with neoadjuvant chemotherapy plus surgery and with surgery alone (Table 27):

- Versus surgery alone: HR 0.52 (95% CrI: 0.41 to 0.65), which represents a reduction in risk of experiencing an event of 48%;
- Versus neoadjuvant chemotherapy: HR 0.59 (95% Credible interval [95% CrI: 0.48 to 0.72), which represents a reduction in risk of experiencing an event of 41%.

The difference between peri-adjuvant pembrolizumab and neoadjuvant nivolumab for EFS did not reach statistical significance, but the direction of effect favoured pembrolizumab (HR 0.87: 95% CrI 0.59 to 1.27; Table 27). MSD note that the 95% CrI for the comparison is wide. The NMA-generated HRs and 95% CrIs for the estimates reflecting comparisons within the KEYNOTE-671 and CheckMate 816 studies are consistent with the HRs and 95% CIs for EFS reported by the pivotal trials (Table 21), as would be expected in a fixed effects model and given that a single study was informing the network for each comparison. Surface under the cumulative ranking curve (SUCRA) analysis, which reports the probability that a treatment has of being among the best options, identified pembrolizumab as having the highest probability of being the most effective treatment, followed by neoadjuvant nivolumab with chemotherapy, neoadjuvant chemotherapy and surgery alone.

Table 27. Summary of results from constant NMA of treatments for the outcome of EFS: fixed effects method

Neoadjuvant chemotherapy	**0.87 (0.79 to 0.97)**	**1.47 (1.07 to 2.02)**	**1.70 (1.39 to 2.08)**
1.14 (1.03 to 1.27)	**Surgery alone**	**1.68 (1.20 to 2.36)**	**1.94 (1.55 to 2.44)**
0.68 (0.49 to 0.94)	**0.59 (0.42 to 0.83)**	**Neoadjuvant nivolumab**	1.15 (0.79 to 1.69)
0.59 (0.48 to 0.72)	**0.52 (0.41 to 0.65)**	0.87 (0.59 to 1.27)	**Peri-adjuvant pembrolizumab**

Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 8.16; Deviance: 5.15.

Abbreviations: CrI, Credible interval; DIC, Deviance information criterion; EFS, Event-free survival; NMA, Network meta-analysis.

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B.2.8.1.3. Uncertainties in the indirect and mixed treatment comparisons

A strength of the NMA is that the evidence informing the network was derived from a robust SLR, which was carried out in accordance with accepted methodology. However, only five relevant studies were identified and two of the comparisons in the network were informed by only one study. The three studies informing the comparison with surgery alone were conducted more than 10 years ago and all were stopped early due to publication of positive results for adjuvant chemotherapy.

Several possible sources of bias were noted across the five RCTs informing the NMA, and the potential impact of each is discussed in more detail below:

- Staging of NSCLC at study entry;
- Histology of NSCLC;
- Study location;
- Disparity in the outcome assessed (PFS, DFS, and EFS).

A key potential source of heterogeneity is the categorisations of stage of NSCLC of the patient populations. As noted in Section B.1.3, stage of cancer has been shown to be a strong prognostic factor, with chance of favourable outcome decreasing with increasing stage. Across the studies, the baseline stage of NSCLC ranged from I to IIIB. KEYNOTE-671 enrolled those with stage II or IIIA/B (T3-4N2), with staging based on the 8th edition of the AJCC. For the remaining four studies, only two reported which system was used to stage NSCLC at baseline — CHEST(54) (5th Edition AJCC) and CheckMate 816(45) (7th Edition AJCC). The disparity and lack of clarity around the staging systems used across the studies makes it challenging to quantify the extent and direction of bias across the network. The inclusion in some studies of those with stage I NSCLC, including CheckMate 816, could mean that those patients would have a more favourable prognosis and lead to more favourable point estimates for EFS than would be seen in studies enrolling patients with stage II and above NSCLC. However, MSD consider that the inclusion of stage I patients introduces minimal bias into the NMA as the proportion of those with stage I NSCLC in each study is likely to be small.

Theoretically, histology could affect baseline prognosis or treatment effect. Across the studies, CheckMate 816 and Felip 2010 enrolled the largest proportions of patients with squamous histology, with 51% of patients having squamous NSCLC (Table 21). By contrast, 43% of patients included in KEYNOTE-671 had squamous NSCLC, with the proportion of squamous NSCLC in the remaining studies ranging from 32% to 41%. However, given the

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difference in proportion of squamous histology between the KEYNOTE-671 and CheckMate 816 populations is only 8%, MSD consider that the difference will have minimal impact on the point estimate generated for the comparison of pembrolizumab and neoadjuvant nivolumab.

Region, particularly East Asia, is considered a key characteristic because of the higher prevalence of EGFR mutations in people with NSCLC and of East Asian ethnicity (prevalence of ~10% in Caucasian versus ~40% in Asian ethnicity).(62) EGFR is the gene with the most frequent mutations in NSCLC. MSD note that testing for EGFR and ALK abnormalities is not routine in early stage NSCLC in clinical practice in England, and that the impact of having these genetic mutations on outcomes in early stage NSCLC has not, as yet, been thoroughly researched. However, with the introduction of treatments for which testing for EGFR and ALK mutations is required, it is expected that testing for these biomarkers will become more common place.

Of the five RCTs informing the NMA, in one RCT (N=270), 99% of patients enrolled were White, and two other studies did not report baseline characteristics by region. CheckMate 816 actively excluded those with EGFR and ALK abnormalities. By contrast, in KEYNOTE-671, although there was some testing for EGFR status, it was not mandatory. Of those tested, 33% of participants had an EGFR mutation, which represented ~4% of the full trial population for KEYNOTE-671, but 30.6% of the trial population were recruited from sites in East Asia, and 31% of patients were categorised as Asian race. Thus, it is possible that the proportion of patients with EGFR mutations is larger than the recorded value. It has been reported that people with EGFR-mutant NSCLC show poor response to immunotherapies targeting PD-L1.(63) Thus, MSD consider that the presence of EGFR+ patients (both observed and unobserved) mean it is possible that there is a degree of bias against pembrolizumab in the indirect comparison versus CheckMate 816, the extent of which cannot be quantified.

Location of trial sites across the studies is another source of heterogeneity, and also impacts the external validity of the trials. As commented by the Evidence Assessment Group (EAG) for TA876 that evaluated neoadjuvant nivolumab plus chemotherapy, the “characteristics of the patients enrolled in CheckMate 816 may not be reflective of patients seen in clinical practice in England” due to around half of participants being enrolled at sites in Asia (47.5% in neoadjuvant nivolumab group vs and 51.4% in the control group).(7) The EAG noted that subgroup analyses for CheckMate 816 by geographic region for EFS were open to imprecision, with neoadjuvant nivolumab plus chemotherapy potentially being more or less

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effective than in the Asian population. MSD acknowledge that KEYNOTE-671 also enrolled few people from the UK (N=10), but consider that, overall, the baseline characteristics of the patient population are more generalisable to patients in the UK likely to be eligible for peri-adjuvant pembrolizumab.

Considering outcomes assessed, two RCTs each reported DFS, PFS and EFS, with the two more recent trials — KEYNOTE-671 and CheckMate 816 — reporting EFS as a primary outcome. For the purposes of the network, the DFS, PFS and EFS have been assumed to be similar. MSD consider the assumption to be appropriate as the most common first event in KEYNOTE-671 was disease progression/recurrence, which is an event common to DFS and PFS. KEYNOTE-671 was a double-blind study, which minimises the risk of bias arising from knowledge of treatment allocation and is particularly important for an outcome that has a subjective component, such as EFS. In contrast to KEYNOTE-671, CheckMate 816 is an open-label study, which may have introduced some bias into the results.

The results of both the fixed and random effects NMAs with time varying HRs replicate the trend of decreasing hazards for pembrolizumab versus chemotherapy (which remain statistically significant at each time point) and increasing hazards for nivolumab versus chemotherapy (which become non-significant after around a year) observed in the clinical trials (see Figure 13). The direct analysis of HR over time for the CheckMate 816 trial indicates that the hazard ratio over time may cross 1. However, HR for neoadjuvant nivolumab versus neoadjuvant chemotherapy crossed 1 from results generated by the NMAs, indicating that estimates from the NMA at later timepoints may be biased in favour of nivolumab. However, MSD also acknowledge that there is a small number of patients at risk at later time points in CheckMate816, which means that the results of the time-varying NMA at later time points should be interpreted with caution.

MSD consider that there are sources of bias in the NMA informing estimates of comparative clinical effectiveness, the overall direction of and impact of which cannot be quantified. However, despite the differences associated with the evidence base informing the networks, MSD note that, all constant and time-varying fixed effect NMAs indicate that pembrolizumab affords a meaningful clinical benefit in EFS compared with neoadjuvant chemotherapy and with surgery alone, with all differences reaching statistical significance. For the comparison with neoadjuvant nivolumab plus chemotherapy, the NMAs indicate that the direction of effect favours pembrolizumab, and support an increasing benefit over time, but no difference is statistically significant.

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B.2.9. Adverse reactions

Summary of adverse events information

- The AE summary profile of the treatment regimen of pembrolizumab plus chemotherapy followed by pembrolizumab monotherapy was generally consistent with the known safety profile of pembrolizumab monotherapy and the known safety profile of the individual chemotherapy components.
- The overall incidence of participants with AEs, drug-related AEs, drug-related Grade 3 to 5 AEs, and drug-related SAEs, were generally similar between the pembrolizumab and placebo arms.
- The pembrolizumab arm had a higher incidence of participants with Grade 3 to 5 AEs, SAEs, discontinuations of any drug due to an AE, and discontinuation of pembrolizumab due to an AE or SAE compared with the placebo arm.
- The incidences of AEs in each category were generally similar between the two treatment arms during the neoadjuvant/surgery phase with the exception of toxicity Grade 3 to 5 AEs, which were higher in the pembrolizumab arm (59.6%) compared with the placebo arm (50.4%).
- In the adjuvant phase the pembrolizumab arm had a higher number of participants with drug-related AEs (56.6%) compared with the placebo arm (34.1%), which is expected for the comparison of active treatment versus placebo in the adjuvant phase.

B.2.9.1. Extent of exposure

The median duration of exposure to study treatments in the combined phases was higher in the pembrolizumab arm ([redacted] days [range: [redacted] days]) compared with the placebo arm ([redacted] days [range: [redacted] days]) (Table 28). [redacted] (Table 29).

Table 28. Summary of drug exposure combined phases (neoadjuvant/surgery plus adjuvant) (APaT population)

	Pembrolizumab[a]	Placebo[a]
Study days on treatment (days)		
n	396	399
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]

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Study days on pembrolizumab/placebo (days)		
n	396	399
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Number of administrations of pembrolizumab/placebo		
n	396	399
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

Treatment includes study drugs, in-study surgery and in-study radiotherapy.

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Abbreviations: APaT, All participants as treated; SD, Standard deviation.

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Table 29. Exposure by duration combined phases (neoadjuvant/surgery plus adjuvant) (APaT population)

Duration of exposure (months)	Pembrolizumab[a]			Placebo[a]		
	n	%	Person-months	n	%	Person-months
>0	396	100	3,904.00	399	100	3,684.60
≥1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

Each participant is counted once on each applicable duration category row.

Duration of exposure is the time from the first treatment date to the last treatment date.

The duration of exposure in person months is calculated as the total of all individual participant duration values in days divided by days per month (1 Month = 30.4367 Days).

Treatment includes study drugs, in-study surgery and in-study radiotherapy.

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B.2.9.2. Summary of adverse events

The overall incidence of participants with AEs during the combined phases in IA2 was similar in the pembrolizumab arm (99.5%) and the placebo arm (98.7%) (Table 30).

Table 30. Adverse event summary: combined phases (APaT population)

	Pembrolizumab[a]		Placebo[a]	
	n	%	n	%
Participants in population	396		399	
with one or more adverse events with no adverse event	394	99.5	394	98.7
with no adverse event	2	0.5	5	1.3
with drug-related adverse events[b]	383	96.7	381	95.5
with toxicity grade 3-5 adverse events	257	64.9	213	53.4
with toxicity grade 3-5 drug-related adverse events	179	45.2	151	37.8
with serious adverse events	165	41.7	133	33.3
with serious drug-related adverse events	73	18.4	58	14.5
who died	26	6.6	15	3.8
who died due to a drug-related adverse event	4	1.0	3	0.8
discontinued any drug due to an adverse event	102	25.8	70	17.5
discontinued any chemotherapy	44	11.1	52	13.0
discontinued pembrolizumab or placebo	85	21.5	38	9.5
discontinued any drug due to a drug-related adverse event	77	19.4	53	13.3
discontinued any chemotherapy	32	8.1	46	11.5
discontinued pembrolizumab or placebo	59	14.9	22	5.5
discontinued any drug due to a serious adverse event	60	15.2	32	8.0
discontinued any chemotherapy	19	4.8	19	4.8
discontinued pembrolizumab or placebo	56	14.1	24	6.0
discontinued any drug due to a serious drug-related adverse event	37	9.3	19	4.8
discontinued any chemotherapy	9	2.3	16	4.0
discontinued pembrolizumab or placebo	35	8.8	12	3.0

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

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

Treatment includes study medications, in-study surgery and in-study radiotherapy.

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

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

Grades are based on NCI CTCAE version 4.03.

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Drug includes pembrolizumab/placebo and chemotherapy.
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B.2.9.3. Most frequently reported adverse events

The AEs that were more likely to occur in the pembrolizumab arm, across the combined phases, were hypothyroidism, rash, fatigue, insomnia, dyspnoea, alanine aminotransferase increased, pruritus, pyrexia, and oedema peripheral. Incidences of other AEs were generally similar between the two arms (Table 31).

Table 31. Participants with adverse events (incidence ≥10% in one or more treatment groups): combined phases (APaT population)

	Pembrolizumab[a]		Placebo[a]	
	n	%	n	%
Participants in population	396		399	
with one or more adverse events	394	99.5	394	98.7
with no adverse events	2	0.5	5	1.3
Nausea	229	57.8	213	53.4
Neutrophil count decreased	174	43.9	170	42.6
Anaemia	169	42.7	166	41.6
Constipation	155	39.1	146	36.6
Fatigue	125	31.6	101	25.3
Decreased appetite	115	29.0	102	25.6
White blood cell count decreased	112	28.3	102	25.6
Vomiting	83	21.0	69	17.3
Diarrhoea	79	19.9	75	18.8
Platelet count decreased	76	19.2	77	19.3
Cough	74	18.7	60	15.0
Dyspnoea	73	18.4	52	13.0
Blood creatinine increased	69	17.4	60	15.0
Rash	69	17.4	34	8.5
Procedural pain	61	15.4	59	14.8
Alanine aminotransferase increased	59	14.9	41	10.3
Asthenia	58	14.6	65	16.3
Pruritus	53	13.4	35	8.8
Dizziness	51	12.9	45	11.3
Insomnia	51	12.9	26	6.5
Pyrexia	50	12.6	32	8.0
Hypomagnesaemia	49	12.4	41	10.3
Aspartate aminotransferase increased	47	11.9	33	8.3
Chest pain	47	11.9	33	8.3
Alopecia	45	11.4	41	10.3

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Headache	43	10.9	42	10.5
Hypothyroidism	43	10.9	6	1.5
Hyponatraemia	41	10.4	36	9.0
Stomatitis	41	10.4	37	9.3
Oedema peripheral	40	10.1	24	6.0
Hypokalaemia	31	7.8	40	10.0
Hyperglycaemia	29	7.3	42	10.5

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

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

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.

Treatment includes study medications, in-study surgery and in-study radiotherapy.

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

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

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B.2.9.4. Drug-related adverse events

The overall incidence of participants with drug-related AEs as determined by the investigators during the combined phases in IA2 was similar between the pembrolizumab arm (96.7%) and placebo arm (95.5%) (Table 32). The incidences of the most frequently reported drug-related AEs (incidence ≥30%) were generally similar between the treatment arms.

Table 32. Participants with drug-related adverse events (incidence ≥5% in one or more treatment groups): combined phases (APaT population)

	Pembrolizumab[a]		Placebo[a]	
	n	%	n	%
Participants in population	396		399	
with one or more adverse events	383	96.7	381	95.5
with no adverse events	13	3.3	18	4.5
Nausea	216	54.5	205	51.4
Neutrophil count decreased	169	42.7	168	42.1
Anaemia	143	36.1	135	33.8
White blood cell count decreased	111	28.0	98	24.6
Fatigue	108	27.3	95	23.8
Constipation	107	27.0	101	25.3
Decreased appetite	92	23.2	89	22.3
Vomiting	76	19.2	58	14.5
Platelet count decreased	74	18.7	75	18.8
Blood creatinine increased	57	14.4	48	12

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Diarrhoea	53	13.4	56	14
Alanine aminotransferase increased	51	12.9	33	8.3
Rash	47	11.9	26	6.5
Asthenia	45	11.4	57	14.3
Alopecia	41	10.4	41	10.3
Pruritus	38	9.6	26	6.5
Aspartate aminotransferase increased	37	9.3	25	6.3
Hypothyroidism	37	9.3	5	1.3
Hypomagnesaemia	35	8.8	22	5.5
Stomatitis	35	8.8	29	7.3
Dysgeusia	30	7.6	36	9
Malaise	29	7.3	27	6.8
Dizziness	24	6.1	22	5.5
Hyponatraemia	24	6.1	17	4.3
Tinnitus	24	6.1	23	5.8
Hiccups	22	5.6	30	7.5
Lymphocyte count decreased	20	5.1	21	5.3

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

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

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.

Treatment includes study medications, in-study surgery and in-study radiotherapy.

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

Database cutoff date of 10 July 2023.

B.2.9.5. Grade 3 to 5 adverse events

The Grade 3 to 5 AEs observed for participants treated with pembrolizumab plus chemotherapy were generally consistent with the known safety profiles of pembrolizumab monotherapy and the known safety profile of the individual chemotherapy components.

The overall incidence of participants with Grade 3 to 5 AEs during the combined phases was higher in the pembrolizumab arm (64.9%) than the placebo arm (53.4%) (Table 33).

The types and frequencies of the most frequent Grade 3 to 5 AEs (incidence ≥1%) during the combined phases were generally similar between the two treatment arms. There were no specific trends noted in the pembrolizumab arm that suggest any new safety concerns.

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Table 33. Participants with grade 3–5 adverse events (incidence ≥1% in one or more treatment groups): combined phases (APaT population)

	Pembrolizumab[a]		Placebo[a]	
	n	%	n	%
Participants in population	396		399	
with one or more adverse events	257	64.9	213	53.4
with no adverse events	139	35.1	186	46.6
Neutrophil count decreased	86	21.7	79	19.8
Anaemia	39	9.8	28	7
White blood cell count decreased	23	5.8	22	5.5
Platelet count decreased	21	5.3	24	6
Pneumonia	19	4.8	17	4.3
Hypertension	16	4	12	3
Pulmonary embolism	14	3.5	9	2.3
Alanine aminotransferase increased	9	2.3	6	1.5
Aspartate aminotransferase increased	9	2.3	2	0.5
Diarrhoea	9	2.3	5	1.3
Decreased appetite	8	2	1	0.3
Dyspnoea	8	2	4	1
Nausea	8	2	6	1.5
Fatigue	7	1.8	4	1
Hypokalaemia	7	1.8	4	1
Hyponatraemia	7	1.8	10	2.5
Hyperglycaemia	6	1.5	3	0.8
Acute kidney injury	5	1.3	3	0.8
Asthenia	5	1.3	4	1
Blood creatinine increased	5	1.3	0	0
COVID-19 pneumonia	5	1.3	0	0
Hyperkalaemia	5	1.3	2	0.5
Lymphocyte count decreased	5	1.3	4	1
Pneumonitis	5	1.3	0	0
Procedural pain	5	1.3	2	0.5
Syncope	5	1.3	5	1.3
Atrial fibrillation	4	1	4	1
Confusional state	4	1	0	0
Dehydration	4	1	1	0.3
Febrile neutropenia	4	1	2	0.5
Hypophosphataemia	4	1	2	0.5
Lipase increased	4	1	1	0.3
Pneumothorax	4	1	4	1
Vomiting	4	1	1	0.3
Pleural effusion	2	0.5	5	1.3

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[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

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

Treatment includes study medications, in-study surgery and in-study radiotherapy.

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

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Grades are based on NCI CTCAE version 4.03.

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B.2.9.6. Deaths due to adverse events

Deaths due to AEs occurred in 26 (6.6%) participants in the pembrolizumab arm and 15 (3.8%) participants in the placebo arm during the combined phases (Table 34). Of these, 22 deaths in the pembrolizumab arm and 11 deaths in the placebo arm occurred in the neoadjuvant/surgery phase, and 4 deaths in the pembrolizumab arm and 4 in the placebo arm occurred during the adjuvant phase.

Of the deaths that were considered causally related to the study drugs (either pembrolizumab, placebo, or chemotherapy), there were 4 (1.0%) deaths in the pembrolizumab arm (atrial fibrillation, immune-mediated lung disease, pneumonia, and sudden cardiac death) and 3 (0.8%) deaths in the placebo arm (pneumonia, acute coronary syndrome, and pulmonary haemorrhage). Three drug-related deaths in the pembrolizumab arm and 3 in the placebo arm were in the neoadjuvant/surgery phase. One drug-related death in the pembrolizumab arm was in the adjuvant phase.

Table 34. Participants with adverse events resulting in death (incidence >0% in one or more treatment groups): combined phases (APaT population)

	Pembrolizumab[a]		Placebo[a]	
	n	%	n	%
Participants in population	396		399	
with one or more adverse events	26	6.6	15	3.8
with no adverse events	370	93.4	384	96.2
Death	3	0.8	1	0.3
Pneumonia	3	0.8	2	0.5
COVID-19	2	0.5	0	0
Pulmonary embolism	2	0.5	0	0
Respiratory failure	2	0.5	2	0.5
Acute myocardial infarction	1	0.3	1	0.3
Acute respiratory distress syndrome	1	0.3	0	0

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Arterial injury	1	0.3	0	0
Atrial fibrillation	1	0.3	0	0
COVID-19 pneumonia	1	0.3	0	0
Cardiac arrest	1	0.3	0	0
Cardio-respiratory arrest	1	0.3	0	0
Cerebrovascular accident	1	0.3	0	0
Condition aggravated	1	0.3	0	0
Immune-mediated lung disease	1	0.3	0	0
Lung neoplasm malignant	1	0.3	0	0
Pulmonary haemorrhage	1	0.3	1	0.3
Pulmonary sepsis	1	0.3	0	0
Sepsis	1	0.3	0	0
Septic shock	1	0.3	1	0.3
Sudden cardiac death	1	0.3	0	0
Acute coronary syndrome	0	0	1	0.3
Acute kidney injury	0	0	1	0.3
Acute respiratory failure	0	0	1	0.3
Cerebral haemorrhage	0	0	1	0.3
Ischaemic cerebral infarction	0	0	1	0.3
Staphylococcal sepsis	0	0	1	0.3
Systemic infection	0	0	1	0.3

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

Every participant is counted a single time for each applicable row and column. Treatment includes study medications, in-study surgery and in-study radiotherapy Serious adverse events up to 90 days of last treatment are included.

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

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B.2.9.7. Other serious adverse events

The serious adverse events (SAEs) observed for participants treated with pembrolizumab plus chemotherapy were generally consistent with the known safety profiles of pembrolizumab monotherapy and the known safety profile of the individual chemotherapy components. There were no specific trends noted in the pembrolizumab arm that suggest any new safety concerns.

The overall incidence of participants with SAEs during the combined phases was higher in the pembrolizumab arm (41.7%) compared with the placebo arm (33.3%) (Table 35).

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Table 35. Participants with serious adverse events (incidence ≥1% in one or more treatment groups) combined phases (APaT Population)

	Pembrolizumab[a]		Placebo[a]	
	n	(%)	n	(%)
Participants in population	396		399	
with one or more adverse events	165	41.7	133	33.3
with no adverse events	231	58.3	266	66.7
Pneumonia	21	5.3	19	4.8
Pulmonary embolism	9	2.3	9	2.3
Anaemia	8	2	3	0.8
Pyrexia	8	2	1	0.3
Aspartate aminotransferase increased	7	1.8	1	0.3
Neutrophil count decreased	6	1.5	1	0.3
Pneumothorax	6	1.5	4	1
Alanine aminotransferase increased	5	1.3	1	0.3
Atrial fibrillation	5	1.3	3	0.8
COVID-19 pneumonia	5	1.3	0	0
Cerebrovascular accident	5	1.3	0	0
Diarrhoea	5	1.3	3	0.8
Pneumonitis	5	1.3	1	0.3
COVID-19	4	1	1	0.3
Immune-mediated lung disease	4	1	1	0.3
Nausea	4	1	5	1.3
Acute kidney injury	3	0.8	4	1
Platelet count decreased	3	0.8	10	2.5
Pleural effusion	3	0.8	7	1.8
Pulmonary air leakage	1	0.3	4	1

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

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

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.

Treatment includes study medications, in-study surgery and in-study radiotherapy Serious adverse events up to 90 days of last treatment are included.

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

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B.2.9.8. Adverse events leading to discontinuation of study treatment

There were no specific trends in discontinuation of study drug due to AEs in the pembrolizumab arm that suggested any new safety concerns.

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The overall incidence of participants with AEs resulting in discontinuation of any study drug during the combined phases was higher in the pembrolizumab arm (25.8%) compared with the placebo arm (17.5%).

The higher incidence of participants with AEs resulting in discontinuation of study drug in the pembrolizumab arm was primarily driven by events that occurred in <1% of participants. The most frequently reported AEs (incidence ≥1%) resulting in the discontinuation of any study drug in the combined phases were:

- Pembrolizumab arm: pneumonitis (1.8%); anaemia (1.5%); neutrophil count decreased (1.5%); aspartate aminotransferase increased (1.3%); blood creatinine decreased (1.0%); diarrhoea (1.0%); and pneumonia (1.0%).
- Placebo arm: nausea (2.0%); neutrophil count decreased (1.8%); blood creatinine increased (1.5%); pneumonia (1.3%); and acute kidney injury (1.0%).

Further details are available in Appendix F.

B.2.9.9. Adverse events resulting in interruption of treatment

There were no specific trends in interruption of study drug due to AEs in the pembrolizumab arm that suggested any new safety concerns.

The overall incidence of participants with AEs resulting in interruptions of any study drug during the combined phases was similar between the pembrolizumab arm (42.7%) and the placebo arm (35.6%).

The most frequently reported AEs (incidence ≥4%) resulting in interruption of any study drug in the combined phases were:

- Pembrolizumab arm: neutrophil count decreased (16.9%); anaemia (4.0%); and white blood cell count decreased (4.0%).
- Placebo arm: neutrophil count decreased (17.0%); and white blood cell count decreased (6.0%).

Further details are available in Appendix F.

B.2.9.10. Adverse events of special interest

No new indication-specific AEOSI was identified (i.e., immune-mediated events causally associated with pembrolizumab) when pembrolizumab was administered concurrently with neoadjuvant chemotherapy and followed by adjuvant pembrolizumab monotherapy (Table

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36). The types of AEOSI observed in the pembrolizumab arm were generally consistent with the known safety profile of pembrolizumab monotherapy.

Table 36. Participants with adverse events of special interest (Incidence >0% in one or more treatment groups) combined phases (APaT Population)

	Pembrolizumab[a]		Placebo[a]	
	n	%	n	%
Participants in population	396		399	
with one or more adverse events	103	26	36	9
with no adverse events	293	74	363	91
Hypothyroidism	43	10.9	6	1.5
Pneumonitis	24	6.1	7	1.8
Hyperthyroidism	20	5.1	8	2
Severe skin reactions	8	2	0	0
Colitis	5	1.3	0	0
Infusion reactions	5	1.3	5	1.3
Hepatitis	4	1	2	0.5
Thyroiditis	4	1	1	0.3
Gastritis	3	0.8	2	0.5
Hypophysitis	3	0.8	0	0
Myositis	2	0.5	0	0
Adrenal insufficiency	1	0.3	0	0
Myasthenic syndrome	1	0.3	0	0
Myocarditis	1	0.3	0	0
Guillain-Barre syndrome	0	0	1	0.3
Pancreatitis	0	0	2	0.5
Uveitis	0	0	1	0.3
Vasculitis	0	0	2	0.5

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.

Every participant is counted a single time for each applicable row and column. Treatment includes study medications, in-study surgery and in-study radiotherapy

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

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B.2.10. Ongoing studies

The pivotal trial for this indication, KEYNOTE-671 is ongoing and the next interim analysis (IA3) is expected when [redacted] deaths have occurred. It is not possible to estimate the timing of when information will become available.

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B.2.11. Interpretation of clinical effectiveness and safety evidence

Despite surgery and chemotherapy for early stage NSCLC frequently being given with curative intent, the probability of recurrence of NSCLC is high, with 30%–55% of people having a recurrence of their disease within 5 years. Moreover, when disease recurs it is frequently at an advanced stage. Novel treatment strategies are needed to maximise the possibility of achieving and maintaining a cancer-free state.

Pembrolizumab, through its mode of action, triggers the body's immune response. Use of pembrolizumab in the peri-adjuvant setting not only amplifies the body's response against micro-metastases but also against tumour cells potentially released during surgery, as well as eliminating any distant micro-metastases that might remain after surgery, all of which results in reducing the probability of recurrence. The clinical effect of peri-adjuvant pembrolizumab on reducing recurrence was demonstrated in KEYNOTE-671, where, compared with neoadjuvant chemotherapy alone, pembrolizumab was associated with a reduction in risk of an event of 41% (HR 0.59; 95% CI: 0.48 to 0.72). The effect of pembrolizumab was consistent across pre-specified subgroups. Moreover, pembrolizumab was associated with a statistically significant improvement in OS (HR 0.72; 95%CI: 0.56 to 0.93).

Additionally, NMAs demonstrated that pembrolizumab affords clinical benefit over surgery alone and neoadjuvant chemotherapy, with results from fixed effects constant and time-varying NMAs all reaching statistical significance. Compared with neoadjuvant nivolumab plus chemotherapy, the results of NMAs consistently generated effect estimates for EFS that favoured pembrolizumab, although no difference reached statistical significance.

Clinical heterogeneity was identified across studies informing the NMA, including CheckMate 816. A key source of heterogeneity that affects the external validity of CheckMate 816 was recruitment of a large proportion of patients from East Asia, which the EAG for TA876 suggested impacted the generalisability of the trial population to patients in the UK. MSD consider that the population enrolled in KEYNOTE-671 is more generalisable to the patient population likely to be eligible for treatment with pembrolizumab in England and Wales. Moreover, KEYNOTE-671 was a well-designed and well-conducted study deemed to have high internal validity, being deemed to have an overall low risk of bias. It is also notable that EFS was statistically significant for all subgroups of interest in KEYNOTE-671 (Figure 8) whereas EFS was not statistically significant in CheckMate 816 for several key subgroups including the PDL1<1%, PDL1 1–49%, stage IB/II, squamous histology, North American and European geographies.(45)

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Attainment of pCR was a key secondary outcome captured in KEYNOTE-671. Neoadjuvant pembrolizumab plus chemotherapy was associated with a significant improvement in the proportion of people achieving a pCR compared with neoadjuvant chemotherapy alone, with rates of 18.1% and 4.0%, respectively. As touched on in Section B.1.3.1, achieving pCR is associated with favourable survival, and clinical experts have informed MSD that those with pCR would most likely not receive adjuvant pembrolizumab, but there would be some patients with pCR who would benefit from continued treatment. However, those not achieving pCR could be considered for additional pembrolizumab in the adjuvant setting. Despite markedly increasing the proportion of people who reach pCR status, over 80% of patients receiving neoadjuvant pembrolizumab did not achieve pCR and would, therefore, likely benefit from continued treatment with pembrolizumab. It is important to reiterate that clinical advisers to MSD agreed that there are insufficient data from clinical trials in the adjuvant setting to enable identification of non-pCR patients who would not benefit from adjuvant treatment, and, therefore achievement or not of pCR will not drive clinical decision making at this time. MSD consider that, as use of peri-adjuvant therapy in early stage NSCLC is a developing area, further research on the use of pCR in decision-making is warranted.

Clinicians at the 2023 clinical advisory board were not sure whether patients achieving pCR would meaningfully benefit from adjuvant immunotherapy. This was principally because recurrence rates in CheckMate 816 were very low and there did not appear to be any difference in recurrence rates among pCR patients between the intervention arms of CheckMate 816 and KEYNOTE-671.

No new safety concerns were identified for pembrolizumab in KEYNOTE-671. The long exposure combined with the overall incidence of AEs, discontinuations due to AEs, and fatal events suggest pembrolizumab in the peri-adjuvant setting had an acceptable tolerability.

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B.3. Cost effectiveness

Summary of key cost effectiveness information

Conclusions of cost-effectiveness analysis:

- Peri-adjuvant pembrolizumab significantly improves EFS and OS compared with surgery alone and chemotherapy plus surgery. The base case ICERs are [redacted]/QALY vs surgery alone, [redacted]/QALY vs neoadjuvant chemotherapy. The model's conclusions are robust to sensitivity analysis with all scenarios having ICERs below [redacted]/QALY.
- Peri-adjuvant pembrolizumab improves EFS compared with neoadjuvant nivolumab plus chemotherapy. The base case ICER is [redacted].

Model structure:

- The model structure is a Markov model with four health states: event free (EF), locoregional recurrence or progression (LR/P), distant metastasis (DM), and death.

Model inputs:

Patient population inputs:

- Adults with untreated resectable NSCLC

Clinical efficacy inputs:

- Transition probabilities from the EF state were modelled by extrapolating data from KEYNOTE-671. The corresponding transitions for comparators external to the trial were derived from network meta-analysis.
- A cure point was imposed from 5-7 years.
- Transition probabilities from the LR/P health state were obtained from several sources including real-world evidence, literature reports and previous technology appraisals.
- Transition probabilities from the DM health state to death were based on market shares and efficacy of first-line treatments for metastatic NSCLC.
- A scenario analysis which applied a stopping rule to pembrolizumab for patients who achieve a pathological complete response was explored.

Utility inputs:

- Utilities for the EF, LR/P and pre-progression DM states were sources from the KEYNOTE-671 trial (EQ-5D-5L mapped to EQ-5D-3L)

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- Utilities for the post-progression DM substate were sourced from the KEYNOTE-189 and KEYNOTE-407 trials.

Costs and resource use inputs:

- Cost inputs were sourced publicly available sources (NHS Reference costs, BNF, eMIT, PSSRU). Resource use estimates were based on the KEYNOTE-671 trial, previous NICE appraisals and clinical expert advice.

Base-case results and sensitivity analyses:

- The model's base case ICER is [redacted]/QALY vs surgery alone, [redacted]/QALY vs neoadjuvant chemotherapy and [redacted]/QALY vs nivolumab plus chemotherapy
- Extensive sensitivity analyses have been conducted.

Scenario analyses:

- Pembrolizumab was highly cost-effective versus the chemotherapy and surgery comparators in all scenario analyses tested.
- Pembrolizumab is cost-effective compared with neoadjuvant nivolumab at a threshold of £30,0000/QALY gained with the exception of some analyses where comparative effectiveness was derived from a time-constant HR from the NMA. In scenarios where a stopping rule is applied to pembrolizumab for patients who achieve a pathological complete response, pembrolizumab was cost-effective at a threshold of £30,000/QALY gained in all scenarios.

Cost effectiveness conclusions:

- No standard structure exists in early NSCLC but the economic model is broadly structurally consistent with models used in recent NICE Technology Appraisals in other early-stage NSCLC indications.
- Direct treatment effects on EFS were informed by a large, high quality RCT and indirect treatment effects were informed by network meta-analyses of RCTs of interventions relevant to UK clinical practice.
- Pembrolizumab is modelled to increase QALYs by both delaying recurrence and increasing the probability that a patient is genuinely cured by their radical treatment plan. The increased cost of peri-adjuvant treatment versus other comparators was offset to a varying extent by the reduced need for treatments and management of recurrent and metastatic NSCLC.

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- Pembrolizumab was highly cost-effective versus standard treatment options in all scenarios. While the base case ICER for pembrolizumab versus nivolumab + chemotherapy was below £20,000/QALY gained, the ICER was above £30,000 in some scenario analyses. Given the relative strength of the clinical evidence supporting each of these two indications, the company believes there is more confidence surrounding the cost-effectiveness of peri-adjuvant pembrolizumab in this multi-comparator decision space compared with neoadjuvant nivolumab.

B.3.1. Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify published studies evaluating the cost-effectiveness of treatments relevant to the decision problem. Full details on the methodology and findings of the SLR are detailed in Appendix G. No economic models evaluating the cost-effectiveness of peri-adjuvant treatments in NSCLC were identified. The only published cost-effectiveness study in the neoadjuvant setting in the UK was the NICE appraisal of nivolumab (TA876).(7) Six further studies were identified in the adjuvant setting: three for atezolizumab and three for osimertinib. Two of these were the NICE appraisals of atezolizumab and osimertinib.(5, 6) As the three identified NICE appraisals were the most comprehensive sources and relevant to the decision problem, these are summarised in the features of the economic analyses in Table 38.

B.3.2. Economic analysis

In the absence of published models in the peri-adjuvant setting, a *de novo* economic evaluation was conducted to assess the cost-effectiveness of pembrolizumab with chemotherapy as a neoadjuvant treatment followed by pembrolizumab monotherapy as an adjuvant treatment for untreated resectable NSCLC.

B.3.2.1. Patient population

The patient population for the current appraisal is aligned with that of the expected marketing authorisation, that is, adults with resectable NSCLC at high risk of recurrence.(1) This reflects the population in the decision problem (Table 1). In addition, the decision problem identifies several subgroups of interest. The subgroup “whether pembrolizumab is used before and after surgery” is explored in scenario analyses whereby it is assumed that patients who achieve a pathological complete response (pCR) after neoadjuvant therapy do not receive further treatment with pembrolizumab. As discussed in section B.1.1, the other

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subgroups included in the NICE scope were not considered relevant to the decision problem and were therefore not explored in the economic evaluation.

The starting age and gender distribution of the model cohort in cycle 0 was based on the reported characteristics of the KEYNOTE-671 trial population (N=797, Table 37). Means and standard errors of body surface area and body weight were also based on the KEYNOTE-671 population. Glomerular filtration rate (GFR) was estimated based on a prior NICE submission for pemetrexed (TA181), which estimated that a target area under the curve (AUC) of 5 would require 500 mg dose of carboplatin on average.(64) 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 37. Baseline characteristics of the patients in the economic model

Characteristic	Value	Source
Starting age (years), mean	63.1	KEYNOTE-671
Female (%)	29.4%	
Body surface area (m^2), mean	1.90	
Body surface area (m^2), standard error	0.01	
Weight (kg), mean	73.7	
Weight (kg), standard error	0.6	
Squamous histology (%)	43.2%	
Non-squamous histology (%)	56.8%	
Glomerular filtration rate (GFR) (mL/min/1.73 m^2)	75.0	NICE TA181

B.3.2.2. Model structure

The 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 have commonly been used for appraisals of treatments with earlier-stage cancer indications in which OS cannot be directly modelled using the available pivotal trial data, including TA876 for neoadjuvant nivolumab in resectable NSCLC,(7) TA761 (adjuvant osimertinib for resected NSCLC)(5) and TA823 (adjuvant atezolizumab for resected NSCLC).(6) A summary of the key features of the *de novo* model, contrasted with these appraisals, is presented in Table 38. Further details of the previous evaluations are presented in Appendix G.

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Table 38. Features of the economic analysis

Factor	Previous evaluations			Current evaluation	
	Adjuvant Osimertinib (TA761)	Adjuvant Atezolizumab (TA823)	Neoadjuvant Nivolumab (TA876)	Chosen values	Justification
Model structure	Markov with five health states (disease free survival, 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 (event free, locoregional recurrence, distant metastasis, Death). 'Payoff' structure used in DM state.	Markov with four health states (event free, local-regional recurrence/progression, distant metastasis, Death). DM costs and utility weighted average of first and second line.	There is no standard approach to modelling early NSCLC. This model structurally reflects the impact of the disease on patients with early NSCLC. Specifically, the health states capture the type of recurrence as the primary endpoint of the KEYNOTE-671 trial (i.e., EFS) which encompasses both types of recurrence events (either local-regional recurrence or distant metastasis). The model captures the key aspects of the clinical pathway and patient experience while adhering to the principles of model parsimony and transparency. In addition, this model structure is broadly consistent with the most recent submission in early-stage lung cancer (TA876). (7) One key difference is the modelling of the DM health state. The exponential rate of DM to death in the model is based on the market share of treatments for metastatic NSCLC and the expected survival associated with each regimen. In contrast, in TA876 one-off LYs, QALYS and costs were applied to patients on chemotherapy,

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					immunotherapy or untreated based on previous NICE technology appraisals.
Time horizon	37 years	40 years	35 years	36.9 years	Lifetime time horizon based on mean age in KEYNOTE-671 of 63.1 years. After 36.9 years, virtually all patients have died and so lifetime costs and benefits are captured in the economic model.
Cycle length	4.35 weeks	1 month	3 weeks	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	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	N/R from the Committee Papers	Not included. Cure point instead.	The rationale for why no treatment effect waning is applied from the EF health state is given in B.3.3.1.1.
Source of utilities	• SF-36 (from ADAURA) mapped to EQ-5D-3L • EORTC QLQ-C30 (from	Various sources identified via an SLR: • Disease-free survival: Jang et al. 2010(66)	EQ-5D-3L data from CM-816 • Base case: EF capped with general population, with	EQ-5D-5L from KEYNOTE-671 mapped to EQ-5D-3L using the Hernandez-Alava mapping algorithm (69)	The EQ-5D-5L from KEYNOTE-671 is the most appropriate data and has been mapped to EQ-5D-3L in line with recommendations in the NICE methods guide.(70)

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	FLAURA) mapped to EQ-5D-3L • EQ-5D-3L estimates from literature (Labbé et al(65))	• Local-regional recurrence: Chouaid et al 2013 (curative)(67), Van den Hout et al. 2006 (palliative) 1L(68) • Metastatic recurrence: IMpower150 2L metastatic recurrence : IMpower150)	LR decrement from CM-816 • Company scenario: unadjusted from trial • EAG scenarios: estimates from literature and clinical expert opinion		
Source of costs	NHS Reference costs (2018/2019), BNF, eMIT	NHS Reference costs (2019/2020), BNF, eMIT	NHS Reference costs (2019/2020, inflated to 2021 values), 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	3.5% to costs and effects	In line with the NICE reference case.

Abbreviations: 1L, first line; 2L, second line; AE, adverse event; BNF, British National Formulary; EAG, Evidence Assessment Group; EF, event-free; HCC, half cycle correction; LR/P, locoregional recurrence or progression; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; N/R, not reported; PSS, Personal Social Services; SLR, systematic literature review.

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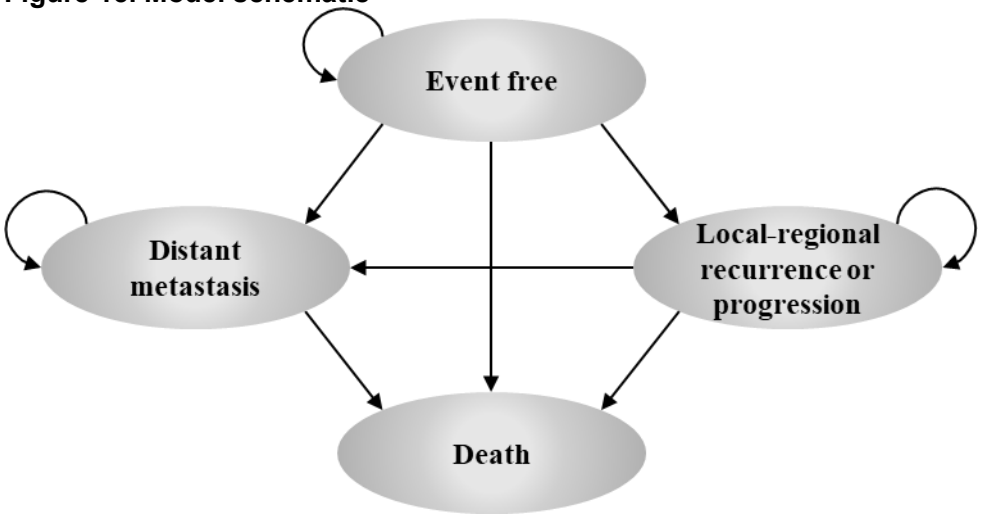
The state transition diagram in Figure 15 illustrates the specific health states and allowable transitions in the Markov model. The model consists of four mutually exclusive health states (i.e., event-free, local-regional recurrence/progression, distant metastases, and death) to track the disease course and survival of patients over time.

This model structure differentiates health states by type of recurrence (either local-regional recurrence/progression [LR/P] or distant metastasis [DM]) as the primary endpoint of the KEYNOTE-671 trial (i.e., EFS) encompasses both types of recurrence event. These two types of recurrence were expected to have different implications on patients' prognosis, health-related quality of life (HRQoL), and disease management, and therefore result in different health outcomes and costs.

Figure 15. Model schematic



All patients entered the model in the EF state following diagnosis of resectable NSCLC, with characteristics consistent with the KEYNOTE-671 trial patient population at baseline. Neoadjuvant and/or adjuvant treatment approach in the EF state (i.e., with pembrolizumab, nivolumab, chemotherapy or surgery alone) affects patients' risks of transitioning directly from EF to LR/P, DM, or death, and of receiving the initial surgery. The base case model is set up to assume that exposure to pembrolizumab provides no continuing therapeutic/treatment effect once a patient has experienced recurrence (LR/P or DM). However, the model somewhat underpredicts the OS benefit that was observed in KEYNOTE-671. To address this in a scenario analysis, functionality was added to temporarily calibrate the downstream transition probabilities in the model so that modelled OS in both arms more precisely matched the trial OS. Further discussion of this scenario is included in B.3.3.1.3.

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In KEYNOTE-671, follow-up imaging data were not routinely collected once patients had experienced LR/P as their first event. This meant it was not possible to obtain LR/P→DM and, consequently, LR/P→death transition probabilities, so external data sources were required to estimate these. Patients in the LR/P 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 and distribution of the specific first-line treatment received for DM.

B.3.2.3 Intervention technology and comparators

In the neoadjuvant setting pembrolizumab was considered in the economic analysis as per the anticipated licensed dosing regimen tested in the KEYNOTE-671 trial (i.e. administered intravenously at a fixed dose of 200 mg every 3 weeks [Q3W]). As per the KEYNOTE-671 trial protocol, patients could receive a maximum of 4 cycles of pembrolizumab in the neoadjuvant setting. Patients also received 4 cycles of neoadjuvant chemotherapy with either cisplatin (75 mg/m^2) and gemcitabine 1,000 mg/m^2 Q3W (in participants with squamous histologic features) or cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) Q3W (in those with non-squamous histologic features). In the adjuvant setting in the clinical trial patients could receive a maximum of 13 cycles of pembrolizumab monotherapy, also at a fixed dose of 200 mg Q3W, or until disease recurrence, toxicities leading to discontinuation, or physician/patient decision. Pembrolizumab can also be administered at a fixed dose of 400 mg Q6W. Clinical advice to MSD indicated that clinicians would prefer to use the Q6W dosing regimen in the adjuvant setting.(71) The model includes the assumption that patients in the adjuvant setting receive 1 cycle of pembrolizumab 200 mg followed by a maximum of 6 cycles of a 400 mg dose Q6W. A Q3W dosing schedule that aligns with the clinical trial is explored in scenario analyses.

The comparators included in the economic model are:

- Neoadjuvant chemotherapy: This was modelled based on the within-trial comparator arm of KEYNOTE-671 (i.e. neoadjuvant placebo + chemotherapy followed by adjuvant placebo)
- Neoadjuvant nivolumab with chemotherapy (“neoadjuvant nivolumab”): This was included in the model as per the treatment regimen studied in CheckMate-816 (and

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NICE TA876(7)) and HR estimates from an NMA of neoadjuvant treatment strategies (see section B.2.8 and B.3.3.1)

- Surgery alone: This was modelled based on HR estimates from an NMA of neoadjuvant treatment strategies (see section B.2.8 and B.3.3.1)

As discussed in B.1.1, osimertinib and atezolizumab were not considered relevant comparators as they are currently available only via the CDF and not through baseline commissioning. Since they are adjuvant therapies, they are also not true comparators to neoadjuvant pembrolizumab at the neoadjuvant therapy decision-making point. Neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab monotherapy was also excluded as the NICE appraisal for this treatment strategy is currently ongoing and, if recommended, would not yet be established clinical practice in the NHS.

B.3.3. Clinical parameters and variables

All patient level data from KEYNOTE-671 were taken from the prespecified IA2, with a database cutoff date of 10th July 2023. The availability of the next KEYNOTE-671 data cut is uncertain as this is event driven (see section B.2.10).

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

The set of allowable transitions and corresponding data sources are summarized in Table 39. The key transition probabilities that are influenced by clinical effectiveness data are the three transitions starting from the EF state (i.e., event-free to local-regional recurrence, event-free to distant metastases, and event-free to death). These transition probabilities were estimated using patient-level data from KEYNOTE-671 for the neoadjuvant pembrolizumab and neoadjuvant chemotherapy arms, and results from a network meta-analysis (NMA) for the neoadjuvant nivolumab and surgery alone arms.

Table 39. Summary of transitions and estimation approaches

Transition(s)	Estimation approach	Data source(s)
EF → LR/P EF → DM EF → Death*	• **Peri-adjuvant pembrolizumab and neoadjuvant chemotherapy**: Parametric multistate modelling approach in which different parametric functions were fitted to each of the three individual transitions starting from EF, accounting for competing risks. • **Neoadjuvant nivolumab and Surgery alone**: Time-varying HRs from an NMA of EFS applied to the overall hazard of EFS failure for the pembrolizumab arm.	• Patient-level data from KEYNOTE-671 • NMA of neoadjuvant treatments • UK national life tables were used as minimum transitions to death and as the only EF→Death transition for cured patients.

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	• A **cure assumption** was applied among patients who achieve long-term EFS. Specifically, the per-cycle risks of transitions from the EF state were gradually reduced by 95% for patients who remain in EF state ≥5 years. This gradual adjustment took place from years 5-7 in the base case.	
LR/P → DM LR/P → Death*	• Exponential competing risks models were fitted using KM data on equivalent patients in the SEER-Medicare database. • Rescaled values were returned to observed values from SEER-Medicare after the available follow-up time in KEYNOTE-671 trial.	• Patient-level analysis of the SEER-Medicare cohort, matched to patients in KEYNOTE-671 (SEER data: 2007-2017; associated Medicare claims data: 2007-2019). • UK national life tables were used for minimum transitions to death.
DM → Death*	• Transition probabilities from DM to death depend upon 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 about when patients in the pembrolizumab arm would be eligible for rechallenge with pembrolizumab (only if recurrence occurred ≥21 months after model start in the base case) and nivolumab (recurrence ≥8 months after model start). • 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	• Market shares based on UK clinical expert opinion • OS and PFS results from KEYNOTE-189/407and other trials in metastatic NSCLC • National life tables - for minimum transitions to death

Abbreviations: CI, confidence interval; DM, distant metastases; EF, event-free; EFS, event-free survival; EMR, electronic medical record; KM, Kaplan-Meier; LR/P, local-regional recurrence or progression; NMA, network meta-analysis; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.
*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.

B.3.3.1.1. Modelling transitions from the event-free (EF) state

The transition probabilities starting from the EF state were estimated based on survival analyses of individual patient-level data from the KEYNOTE-671 trial, following the parametric multistate modelling approach described by Williams et al. (2017a & 2017b).(72, 73) Parametric models were used to estimate the cause-specific hazards of each transition

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over time within the pembrolizumab and placebo arms of the trial. Within each weekly cycle of the model, the probability of each of these transitions (as well as the composite probability of any EFS failure event) was calculated as a function of all three cause-specific hazards. Transition probabilities for the neoadjuvant nivolumab and surgery alone comparators were estimated based on a network meta-analysis (NMA) comparing different neoadjuvant treatment strategies (see section B.2.8).

Estimation of cause-specific hazards for each individual transition starting from the event-free (EF) 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 EFS failure, the two competing failure types were treated as censoring events.(74, 75) For example, to model the transition from EF to DM, patients who experience a LR/P or death prior to DM 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 three parametric modelling approaches were used to explore uncertainty in the estimation of cause-specific transition probabilities starting from the EF state, consistent with the methods applied in NICE TA766, TA837 and TA830:(76-78)

- 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-671 trial. The full suite of seven parametric functions was considered for each transition from the EF state (i.e. EF→LR/P, EF→DM, EF→death).
- Approach #2: Parametric proportional hazards models with treatment arm variable: 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), incorporating a time-constant binary indicator of 1 in the pembrolizumab arm and 0 in the chemotherapy arm. The models thus assumed a time-constant hazard ratio (HR) for pembrolizumab versus placebo in KEYNOTE-671. Accelerated Failure Time models were not explored in this sensitivity analysis for computational simplicity.
- Approach #3: Parametric proportional hazards models with piecewise fittings (before and after year 1): Transition probabilities in the pembrolizumab and placebo arms were

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estimated based on jointly fitted models from the proportional hazards class and used a time-varying HR for pembrolizumab versus placebo. Specifically, 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 HR for during and after the first year following initiation of neoadjuvant therapy (i.e. protocol-defined maximum treatment duration of 1 year).

Parameter estimates associated with each parametric model for Approaches #1–3 are presented in Appendix M. For each of the model arms, probabilities of each transition from the EF state were calculated based on all three cause-specific hazard functions. The predicted EFS curve over time in each treatment arm similarly depended upon all three cause-specific hazard functions. Therefore, in order to select base-case parametric functions, 397 (i.e., 7×7×7 + 3×3×3 + 3×3×3) possible combinations of parametric functions for EF→LR/P, EF→DM and EF→death were considered (see Appendix M). Criteria for selection of the base case parametric functions are described in the following sections.

Calculation of transition probabilities based on cause-specific hazards

For each individual transition starting from the EF 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 EFS failure. The following calculation steps were performed:

1. For each cause of EFS failure *k* (i.e., LR/P, DM, 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 EFS 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 EFS failure was derived as:

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

This represents the probability of having had an EFS failure of type *k* given that an EFS failure has occurred within the cycle.(79) The relative contribution of cause *k* was then multiplied by the probability of any EFS failure within the cycle to obtain the transition probability corresponding to cause *k*.

Within each cycle, the transition probability from EF→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. Mortality rates by age for men and women in the UK were sourced from the Office for National Statistics (ONS) life tables 2020-2022.(80)

Selection of base-case parametric models for transitions from EF state

As noted by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19, assessing model fit is more challenging in the context of multistate models than partitioned survival models, as the target outcomes of interest (e.g., the proportions of individuals experiencing the composite endpoint) are determined by a combination of survival models rather than by a single survival model.(74) As such, to select base case parametric functions for each cause-specific transition, all 397 combinations of functions were considered. Further, in accordance with recommendations in NICE DSU TSD 14, and in the absence of strong evidence to the contrary, base-case parametric functions were selected such that the same functional form was used to model each health state transition in all treatment arms.(81) The appropriateness of the base case parametric functions was assessed using the following criteria:

- *Statistical fit, based on mean squared error (MSE) vs observed EFS*
  Akaike information criterion (AIC), a fit statistic commonly used in partitioned survival models, is not a suitable measure of fit with observed data when modelling competing risks,(72) as in the current Markov model. MSE was therefore used as an alternative diagnostic test to assess fit of the predicted EFS curve versus the observed Kaplan-Meier curve during the within-trial period in each treatment arm. MSE was calculated based on the average of the squared difference in predicted versus observed EFS at weekly intervals across the within-trial period, with weighting by number of patients at risk in each weekly interval.

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In addition, the assumption of proportional hazards was assessed through formal statistical tests to evaluate the potential suitability of Approach #2. Namely, for each transition, the function cox.zph() in R was used to test for independence between time and the scaled Schoenfeld residuals from a Cox proportional hazards model with a time-constant treatment covariate. It is not possible to reject the proportional hazards assumption if the test shows a non-significant relationship between residuals and time.

- *Visual assessment of fit versus observed DFS:*
  Predictions generated by different combinations of parametric functions were visually verified against the observed data in each trial arm, following the approach used by William et al.(2017).(72) Specifically, predicted versus observed cumulative incidence curves were plotted for each of the three individual transitions starting from the EF state. The resulting predictions of EFS as a composite endpoint were also compared against the observed EFS Kaplan–Meier curve in each arm.

- *Clinical plausibility of long-term extrapolations (external validity)*:
  Longer-term extrapolations of EFS and OS for neoadjuvant chemotherapy were externally validated against observed Kaplan–Meier curves from a real-world cohort of US patients with completely resected stage II, IIIA, or IIIB NSCLC (N=221) within the SEER-Medicare administrative claims and linked cancer registry database (2007-2019). The real-world cohort included patients with stage II, IIIA, or IIIB NSCLC who initiated neoadjuvant chemotherapy and subsequently underwent a lobectomy, pneumonectomy, or wedge resection within 90 days of the end of neoadjuvant therapy (i.e. matched to KEYNOTE-671 characteristics). The SEER Medicare cohort was slightly older compared with the KEYNOTE-671 population but was well-matched in terms of staging and histology.
  Although external data sources were unavailable for the neoadjuvant pembrolizumab + chemotherapy / adjuvant pembrolizumab arm, the clinical plausibility of the predicted OS benefit for this perioperative treatment strategy (vs neoadjuvant chemotherapy) was assessed based on the observed OS Kaplan–Meir curves from KEYNOTE-671.

The selection process started with a total of 397 candidate combinations, including 343 under Approach #1, 27 under Approach #2, and 27 under Approach #3. Full details of each step in the selection process are provided in Appendix M.1.2; a summary is provided here:

1. **Statistical fit of EF→death, based on MSE**: This transition had the fewest events observed in the trial, so was selected first to optimise fit and thus filter the number of candidate combinations to a more manageable number. Fit in the neoadjuvant

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chemotherapy arm was typically poorer (i.e., higher MSEs) than in the pembrolizumab arm, therefore this arm was prioritised in the selection process to minimise the overall uncertainty. Combinations under Approach #1 using log-normal for EF→death, or using Gompertz under Approaches #2-3, had the lowest MSEs on average in the neoadjuvant chemotherapy arm. In the pembrolizumab arm, combinations using Approach #1 log-normal ranked third overall based on MSE, but the differences in MSE between each set of combinations were extremely small and did not produce a meaningful difference in curve fit to the observed data. The subsequent steps therefore focused on the 67 combinations of distributions for EF→LR/P and EF→DM that used these distributions for EF→death.

2. **Visual fit of observed vs predicted curves:** Predicted vs observed cumulative incidence for each cause-specific transition, and overall EFS, was assessed for the 67 remaining combinations from Step 1. Visible best fit was noted for the 16 combinations under Approach #1 that used generalised gamma, Gompertz, log-normal or log-logistic for EF→LR/P and EF→DM, and the two combinations under Approaches #2-3 that used Gompertz for both transitions. Thus, visual inspection led to the exclusion of all but 18 combinations of parametric distributions under Approaches #1-3.

3. **Statistical fit:** Consistent with findings from visual assessment, 17 of the remaining 18 combinations after Step 2 ranked within the top 50% of best-fitting combinations (out of the 67 combinations) in both arms based on MSE for predicted vs observed EFS; only Gompertz / Gompertz / Gompertz under Approach #3 had poor MSE ranking and was excluded. The proportional hazards assumption could not be rejected for EF→LR/P (p=0.833) or EF→DM (p=0.366) but was rejected for EF→death (p=0.047). Thus, Gompertz / Gompertz / Gompertz under Approach #2 was also excluded from further consideration. Long-term predictions of EFS and OS did not substantially vary across the remaining 16 combinations; final selection therefore focused on the 8 combinations that were in the top 10 best-fitting in both arms.

4. **Clinical plausibility (external validity):** Predicted EFS in the chemotherapy arm for these 8 combinations was closely aligned with long-term EFS data from the SEER-Medicare cohort. Predicted OS slightly exceeded observed SEER-Medicare OS until year 5 in all combinations, after which the numbers at risk were small. Across all 8 combinations, the estimated incremental EFS benefit of pembrolizumab versus

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chemotherapy was closely aligned with the observed benefit in KEYNOTE-671, whilst the observed incremental OS benefit was underpredicted. As the magnitude of this was similar across candidate distributions, no further exclusions were made based on external validation.

Base case

Based on the assessments described above (and further details provided in Appendix M) and in line with the guidance provided in NICE DSU TSD 14,(81) parametric models separately fitted to each treatment arm (Approach #1; independently fitted models) were preferred. When patient-level data are available, this approach is often preferred as it avoids reliance on an assumption of proportional hazards which is required for Approach #2 (constant proportional hazards) and involves fewer assumptions than are required for applying a time-varying treatment effect (Approach #3; proportional hazards with time-varying treatment effect).

Of the 8 finalist combinations of distributions, the **generalized gamma / generalized gamma / log-normal combination under Approach #1** was selected for the base-case based on its high MSE ranking with respect to EFS. Out of the 67 combinations of distributions that remained after Step 1, the base-case combination was the 1st best-fitting in both arms. Out of the original 397 candidate combinations, this combination was the 1st best-fitting in the neoadjuvant chemotherapy arm and the 5th best-fitting in the pembrolizumab arm. Alternative combinations of parametric functions, including the use of Approaches #2 and #3, were tested in scenario analyses to explore the uncertainty in the extrapolations (Table 40). The long-term EFS and OS projections for the base case combination are presented in Figure 16 and Table 41.

Table 40. Selected approach to modelling transitions from EF health state

	Parametric distribution			Justification
	EF→LR/P	EF→DM	EF→death	
Base case (Approach #1)	Gen gamma	Gen gamma	Log-normal	Best fitting combination in both arms, conservative incremental benefit, and good clinical plausibility
Scenario (Approach #1)	Gen gamma	Gen gamma	Gen gamma	EF→death distribution with the lowest MSE in the pembrolizumab arm
Scenario (Approach #1)	Gompertz	Gen gamma	Log-normal	Second best fitting combination in chemotherapy arm, conservative incremental benefit, and good clinical plausibility

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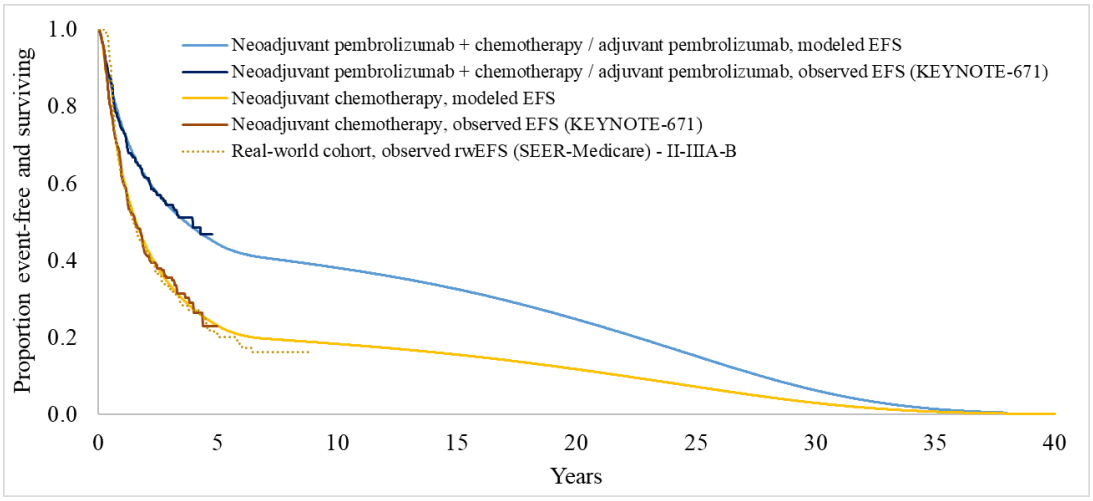
Scenario (Approach #1)	Gen gamma	Gompertz	Log-normal	Second best fitting combination in pembrolizumab arm, conservative incremental benefit, and good clinical plausibility
Scenario (Approach #2)	Gompertz	Gompertz	Gompertz	The only combinations providing plausible fits under Approaches #2-3.
Scenario (Approach #3)	Gompertz	Gompertz	Gompertz	

Abbreviations: DM, distant metastases; EF, event-free; LR/P, loco-regional recurrence or progression. Approach number is shown in parentheses.

Figure 16. Predicted survival estimates with selected parametric functions in the base case analysis

A) EFS



N at risk by year:	0	4	5	8
Pembrolizumab	397	38	-	-
Neoadjuvant chemo	400	20	2	-
SEER-Medicare	221	39	26	12

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B) OS

N at risk by year:	0	4	5	8
Pembrolizumab	397	71	6	-
Neoadjuvant chemo	400	44	5	-
SEER-Medicare	221	69	52	22

Abbreviations: EFS, event-free survival; OS, overall survival.
Note: The predicted OS curves shown in (B) are the combined result of all transition probabilities in the Markov model and are not fitted directly to KEYNOTE-671 OS data. They are the result of using the base-case distributions of EF→LR/P, EF→DM, and EF→death, base-case inputs determining DM→death, and real-world estimates of LR/P→DM and LR/P→death in all arms. Of note, the Kaplan-Meier estimates at the tail of the observed EFS and OS curves from KEYNOTE-671 and the real-world SEER-Medicare study are based on heavily censored data. The curves from this point are not stable and should be interpreted with caution; the numbers of patients at risk are reported at selected time points below each graph.

Table 41. Base case predicted survival estimates

Outcome	Survival by year, %										
	1	2	3	4	5	6	7	10	20	30	40
Neoadjuvant chemotherapy											
EFS	63%	44%	34%	27%	23%	21%	20%	18%	12%	3%	0%
OS	[redacted]										
Pembrolizumab											
EFS	75%	62%	54%	48%	44%	42%	41%	38%	25%	6%	0%
OS	[redacted]										

Abbreviations: EFS, event-free survival; OS, overall survival.

Comparative effectiveness

Transition probabilities for peri-adjuvant pembrolizumab and neoadjuvant chemotherapy were obtained directly from patient-level data within the KEYNOTE-671 trial, as described earlier in this section. However, head-to-head data on the comparative efficacy of peri-adjuvant pembrolizumab versus neoadjuvant nivolumab and surgery alone were not available from the trial.

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Instead, for these comparators, cause-specific hazards of transitioning from the EF health state were obtained from a NMA of clinical trials conducted in the neoadjuvant setting (Table 42), as described in section B.2.8.

The comparative effectiveness was modelled by applying the per cycle time-varying HR for nivolumab and surgery, respectively, versus pembrolizumab to the overall hazard of any EFS failure event in the pembrolizumab arm. To obtain the cause-specific hazards of each transition (i.e., EF→LR/P, EF→DM, and EF→death), the model assumed that the proportion of the overall hazard attributable to each EFS failure type is the same as in the pembrolizumab arm. The HR beyond 5.2 years (the end of the observed trial data) was held constant to prevent the possibility of any implausible HR values being modelled in the extrapolated part of the EFS curve. Scenarios were explored where this hold was removed and where the HR was set to trend to 1 between 5-7 years.

The resulting estimated EFS and OS curves for each arm of the model are illustrated in Figure 17.

Table 42. Hazard ratios of EFS failure versus peri-adjuvant pembrolizumab from NMA

Comparator	Time-constant HR vs pembrolizumab		Time-varying HR NMA parameters (Weibull fixed effects)				
	HR	SE of ln(HR)	d0 estimate	d0 variance	d1 estimate	d1 variance	correlation
Peri-adjuvant pembrolizumab	1	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoadjuvant nivolumab	1.15	0.19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery alone	1.94	0.12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EFS, event-free survival; HR, hazard ratio; NMA, network meta-analysis; SE, standard error.

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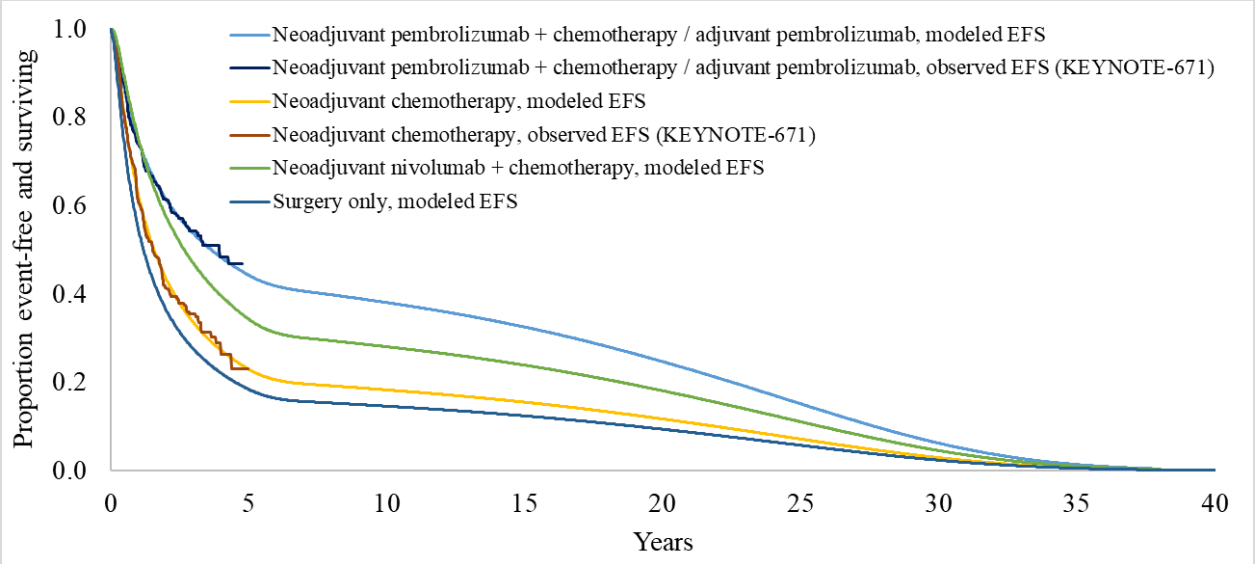
Figure 17. Estimated EFS and OS curves by model arm

A) EFS (base case)



B) OS

[redacted]

Abbreviations: EFS, event-free survival; OS, overall survival.
Cause-specific hazards of transition for neoadjuvant nivolumab and surgery alone are estimated based on time-varying HR NMA results versus peri-adjuvant pembrolizumab.

Cure point

The model allows a cure period to be implemented whereby the per-cycle risk of recurrence or progression (movement to both LR/P and DM) from the event-free state is reduced by 95% relative to the parametric function; 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 EF to death, subject to the constraint that this risk must always be at least as

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high as background mortality. This approach, along with a 95% cure proportion, was also used in TA761 and TA876.

The base-case assumes a cure period from 5 to 7 years. This is based on clinician feedback from the 2022 and 2023 advisory boards which suggested that most relapses occur in the first 5 years and that it is reasonable to assume that there will be very few, if any, recurrences or disease-related deaths after 5 years,(36, 71) as well as published evidence.(82) This is reflected in the typical duration of follow-up for patient monitoring in clinical practice and is also consistent with the feedback from clinical experts elicited in both the neoadjuvant setting for nivolumab (TA876) and the adjuvant setting for atezolizumab (TA823) and osimertinib (TA761).(5-7) 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).(5) 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 this was smoothed out by linearly increasing the cure proportion between 5-7 years.(83) To reflect this, EF 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 can be considered conservative given the consistent clinical feedback across all (neo)adjuvant appraisals; a narrower cure period with 100% risk reduction could be just as plausible, and so was examined in sensitivity analyses.

The assumption is also consistent with the shape of the observed KEYNOTE-671 EFS and OS data – Kaplan-Meier curves where declining hazards are observed and curve 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 EF health state

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

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- 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.(76, 77, 84) It was explored in TA830 where cure assumptions were not applied,(78) and was examined in sensitivity analysis in TA823 but no details on the committee's preferences are available in FAD.(6) Similarly, it was not applied in the NICE appraisal for neoadjuvant nivolumab for early-stage NSCLC.(7)

- TEW is already effectively being applied after the cure-point as hazards are equalising. TEW is justified when the hazards of progression events are thought to no longer differ between arms and the convention across metastatic oncology 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).(85) In KEYNOTE-671, pembrolizumab is administered up to approximately 15 months and follow up data is currently available to 36.6 months. In the current model, the hazards begin to equalise from 5 years (i.e. 3.75 years after treatment cessation) due to the cure assumptions applied (see Figure 18). It is worth noting that there is no evidence to support either the existence or the timing of TEW in immunotherapy. Given all patients in this indication have been treated with curative intent, a cure assumption is a more logical, evidence-based way to equalise the long-term hazards between the arms.

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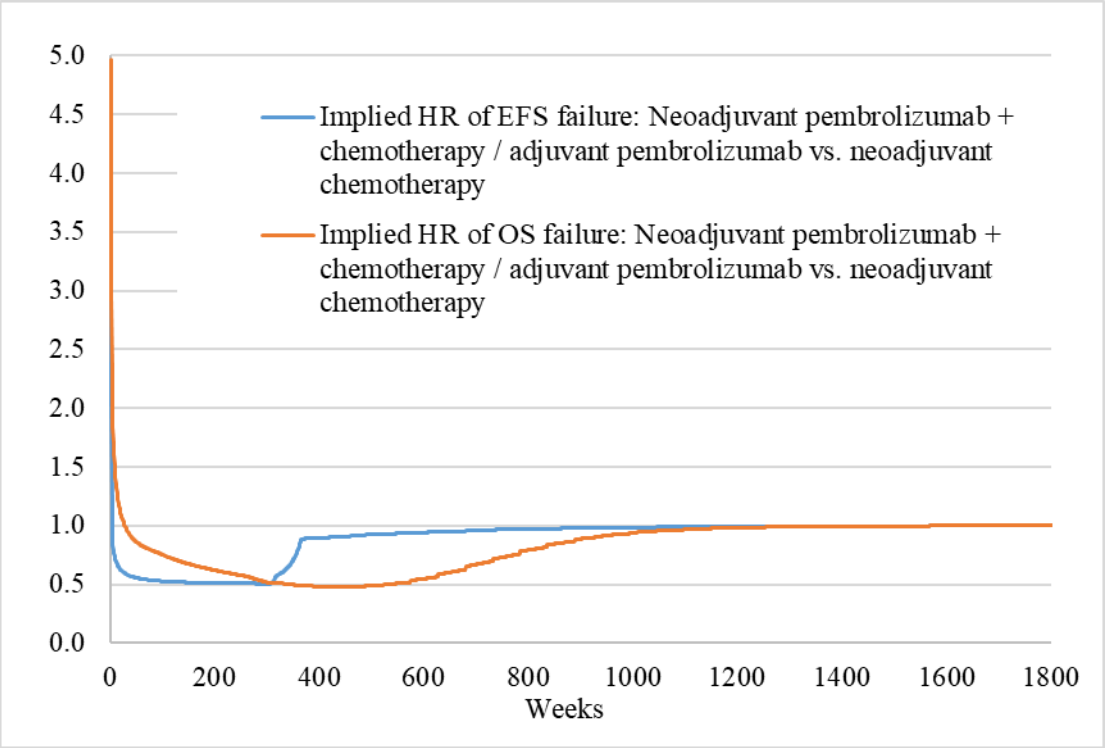
Figure 18: Implied HR or pembrolizumab versus chemo showing equalizing of hazards following imposition of cure point



- <u>The mechanism of action of pembrolizumab supports a sustained treatment effect.</u>
  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.(86)

- <u>Observed KEYNOTE-671 trial data supports a sustained treatment effect.</u>
  The KEYNOTE-671 data show a sustained separation in EFS and OS curves, so a post-discontinuation treatment effect is plausible. In addition, the EFS HR appears to be trending downwards over time, if anything, indicating maintenance of treatment effect beyond treatment cessation at approximately 15 months (Figure 13).

- <u>Long-term data from historic pembrolizumab adjuvant (and other) indications support a sustained treatment effect.</u>
  Longer term data from other KEYNOTE clinical trials have shown a continued treatment effect post-discontinuation of pembrolizumab treatment in both early and late-stage disease. Some example indicative studies include:

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- In KEYNOTE-522, a trial of neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab monotherapy versus neoadjuvant chemotherapy (comparable to the regimen in KEYNOTE-671) for early-stage triple-negative breast cancer, the HR for EFS 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(87, 88)

- 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)(89)

- 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.(90) 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(91, 92)
- 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(93-95)

B.3.3.1.2. Modelling transitions from local-regional recurrence or progression (LR/P) state

In KEYNOTE-671, follow-up imaging data were not routinely collected once patients had experienced local-regional recurrence or progression as their first event. As a result, the subsequent direct transitions from LR/P to DM or death were unavailable from the trial. This is a consequence of trial design in this setting and consistent with previous neoadjuvant and adjuvant NSCLC appraisals, such as those for atezolizumab, osimertinib and nivolumab.(5-7) Therefore, external data sources were explored (Table 44).

In the base case, transitions from the LR/P health state were estimated based on analyses of real-world data from the US SEER-Medicare database. Patients in the SEER Medicare dataset who aligned with the KEYNOTE-671 population (i.e. patients with resectable stage

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II-IIIB[N2] NSCLC, received neoadjuvant treatment, and who were recorded as having a local-regional recurrence or progression event at least 30 days prior to any metastatic occurrence) were included (hereafter referred to as “SEER Medicare KN671-matched”). Full details of the inclusion criteria and baseline characteristics of the SEER Medicare KN671-matched cohort are detailed in Appendix M2. In total, 221 patients met the criteria and of these, 43 were subsequently identified as having a local-regional recurrence/progression at least 30 days prior to any metastatic occurrence and thus were included in the transition probability estimation for LR/P→DM and LR/P→death.

Transition probabilities from local-regional recurrence

Of these 43 patients, exponential competing risks models were then fitted to the cause-specific transitions from LR/P→DM and LR/P→death. The exponential distribution is commonly used to model transition probabilities from intermediate health states in a Markov model, as the hazard rates do not depend on time since entry into the health state. To use more complex parametric approaches to model these transitions would require thousands of tunnel states which would substantially increase the computational burden of the model. When the cause-specific hazards were modelled, patients were followed from the time of loco-regional recurrence/progression and were censored at the earliest of the competing event (DM or death) or end of follow up. As in the EF state, the transition probability from LR/P to death was constrained to be at least as high as background mortality in each weekly cycle. The cause-specific hazards of LR/P→DM and LR/P→death as estimated based on SEER Medicare KN671-matched data are summarised in Table 43.

Table 43. Parameters used to model transitions from LR/P health state

	LR/P→DM		LR/P→death	
	Weekly exponential rate	**SE**	**Weekly exponential rate**	**SE**
SEER Medicare KN671-matched cohort (per weekly cycle)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastases; LR/P, local-regional recurrence or progression; SE, standard error.
Note: The transition probability from LR/P→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/P transition rates

The LR/P 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

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source as summarised in Table 44. These medians were converted to a weekly rate assuming exponential distribution. These sources included:

- In the NICE appraisal for nivolumab (TA876), transitions from LR to DM were modelled based on clinical expert opinion that the annual probability of this transition was 20%, after the experts advised that transitions derived from the LuCaBIS study (Chouaid et al, 2018)(96) were implausibly low.(7)
- In the atezolizumab NICE submission (TA823), transition probabilities from the LR state to DM and death were calculated based on two small single centre studies from Japan and the USA, Nakamichi et al. (2017)(97) and Kruser et al. (2014).(98) Nakamichi et al. (2017) analysed 74 NSCLC patients with postoperative LR events who received chemoradiotherapy or radiotherapy, whilst Kruser et al (2014) included 37 NSCLC patients who received radiotherapy following locoregional recurrence. Moore et al. (2020)(99) 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 locoregional 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.(4)

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Table 44. Alternative sources to model transitions from LR/P health state

Sources	Progression (LR/P→DM)		Overall survival (LR/P→Death)	
	Median progression, months	Estimated weekly rate	Median OS, months	Estimated weekly rate
Used in the base-case				
SEER Medicare KN671-matched	N/A	[redacted]	N/A	[redacted]
Other external sources				
LuCaBIS, Chouaid et al, 2018(96)	N/R	0.0016	N/R	N/R
Clinical expert opinion (TA876)(7)	N/A	0.0043	N/R	N/R
CancerLinQ database analysis (TA761)(5)	15	0.0106	N/R	N/R
Nakamichi et al, 2017; CRT or RT (TA823)(6)	11.6	0.0137	34.4	0.0046
Nakamichi et al, 2017; CRT only (TA823)(6)	19	0.0084	79.6	0.0020
Kruser et al, 2014 (TA823)(6, 98)	N/R	N/R	5.1	0.0314
PACIFIC trial, durvalumab arm (TA798)(4)	24.9	0.0064	63.1	0.0025
PACIFIC trial, placebo arm (TA798) (4)	5.5	0.0290	29.6	0.0054
Moore et al, 2020, curative(99)	N/R	N/R	34.3	0.0047
Moore et al, 2020, palliative(99)	N/R	N/R	9.8	0.0163

Abbreviations: DM, distant metastases; LR/P, local-regional recurrence or progression; N/R: not reported; OS, overall survival.

Notes: Medians reported in the literature 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 Kaplan-Meier (Figure 26 in the company submission) in TA761. Monthly rates are converted to weekly rates by dividing by (365.25/12/7).

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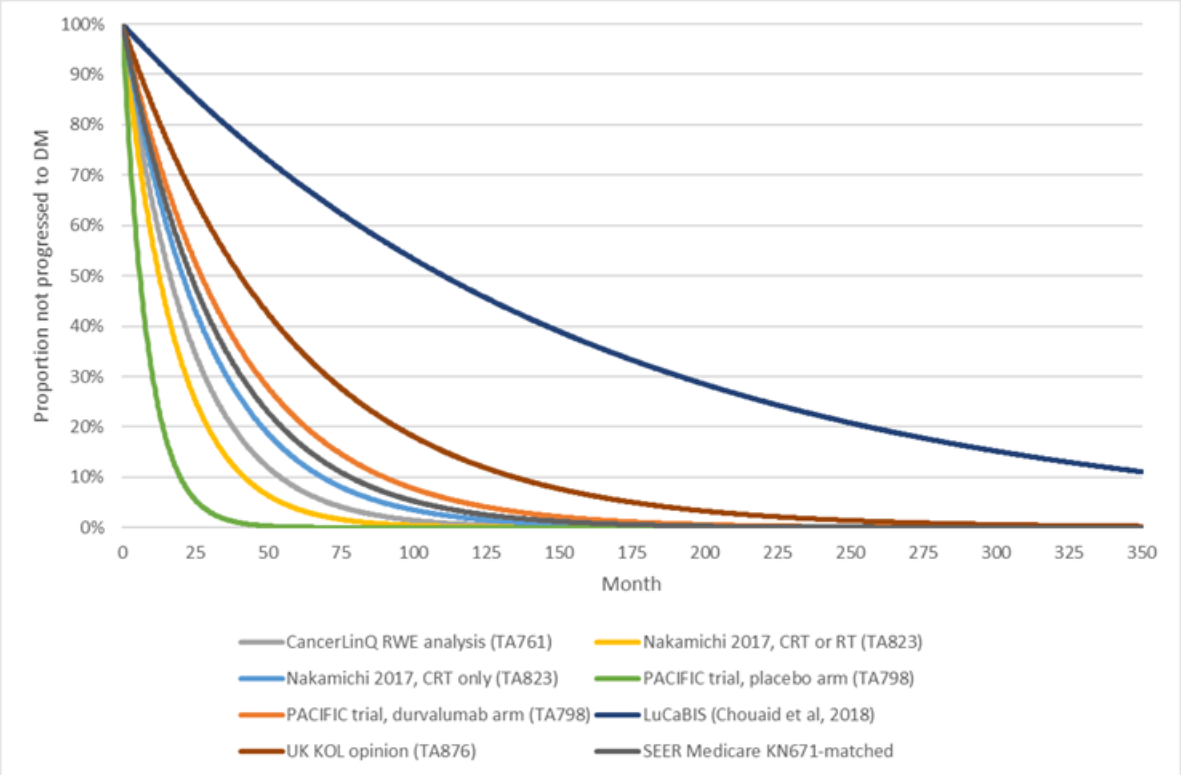
The implied LR/P→DM exponential curves for each of these sources are illustrated in Figure 19. This shows that there is a wide range of transition estimates across the different sources, which may reflect differences in patient characteristics, prior treatment for early-stage disease (e.g. adjuvant vs neoadjuvant therapy), and post-recurrence treatment patterns. The SEER Medicare KN671-matched dataset produces a transition rate that broadly represents a middle-ground estimate, and is quite closely aligned to the durvalumab arm of the PACIFIC trial (TA798) and the curative intent (i.e. CRT) cohort in the Nakamichi et al, 2017 study.(4, 97) At the 2023 Clinical Advisory Board, the advisers were presented with a range of options (excluding the UK KOL opinion from TA876 to minimise risk of bias). They confirmed that none of these datasets can be considered wholly reliable due to lack of generalisability of the patients or outcomes captured.(71) The SEER Medicare KN671-matched cohort was selected for the base case as it was considered the most representative of the patient cohort in KEYNOTE-671.

Figure 19. Other external sources for LR/P to DM movement (converted to weekly probabilities)



Abbreviations: CRT, chemoradiotherapy; DM, distant metastases; KOL, key opinion leader; LR/P, loco-regional recurrence of progression; RT, radiotherapy; RWE, real-world evidence.

B.3.3.1.3. Modelling transitions from distant metastases (DM) state

In each treatment arm, the transition probability from DM to death was assumed to depend on the distribution of first-line treatments for metastatic NSCLC received in that arm. The

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model also considered the cost of second-line therapies for metastatic NSCLC in each arm; however, survival within the DM 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.

Subsequent treatment market shares in distant metastases (DM) health state

First- and second-line treatment proportions for patients who have progressed to the DM state were informed based on advice received from clinicians in the 2022 Clinical Advisory Board,(36) 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 neoadjuvant or adjuvant IO. We therefore assumed that no patients were contraindicated to IO treatments downstream, for example, by having autoimmune conditions.

First line

The 2022 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) IO if relapse had taken place ≥6 months after the end of treatment with adjuvant IO (in this case, peri-adjuvant pembrolizumab or neoadjuvant nivolumab).(6, 36) This criterion is also now included in the relevant Blueteq forms for metastatic IO treatments.(100) The treatment proportions applied in the model are summarised in Table 45:

- IO-eligible: patients who have never received peri-adjuvant pembrolizumab or neoadjuvant nivolumab (i.e., neoadjuvant chemotherapy and surgery alone arms) or who transition to DM state at least 6 months after the final scheduled dose of IO (pembrolizumab arm: 21 months after the start of the model, including 3 month pre- and post-surgery treatment free period; nivolumab arm: 8 months after the start of the model)
- IO-ineligible: patients in the pembrolizumab or nivolumab arms who transition to DM state within 6 months of the final scheduled dose of IO (i.e. pembrolizumab arm: <21 months after the start of the model; nivolumab arm: 8 months after the start of the model)

In both IO-eligibility categories (and in all treatment arms) in first line, 15% of patients are assumed to receive a targeted treatment for NSCLC positive for markers such as EGFR

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KRAS G12C, ALK, or ROS-1. All these mutation types have targeted treatment recommendations in the first-line setting. 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).

In the IO-eligible category, the remaining patients who do not receive targeted therapies (i.e. 85%) are split as follows:

- PD-L1 TPS ≥ 50% (33.4% in KEYNOTE-671): Receive IO monotherapy, assuming an 80:20 split between pembrolizumab and atezolizumab(36)
- PD-L1 TPS <50%: (66.6% in KEYNOTE-671):
    - *Non-squamous (56.8% in KEYNOTE-671; note that all patients receiving TKI are assumed to be non-squamous and are therefore subtracted from this proportion in the market share calculations. After adjusting for TKI-treated proportion = 41.8%):* Receive pembrolizumab with platinum doublet chemotherapy (PDC; pemetrexed + platinum)
    - *Squamous (43.2% in KEYNOTE-671; After adjusting for TKI-treated proportion = 58.2%)*: Receive pembrolizumab with chemotherapy (pembrolizumab + carboplatin + [nab-]paclitaxel)

In the IO-ineligible category, it is assumed that the remaining patients who do not receive a TKI (i.e., 85%) are treated with chemotherapy based on the distribution of squamous (43.2%; carboplatin + [nab-]paclitaxel) vs non-squamous (56.8% minus 15% for TKI use = 41.8%; PDC; pemetrexed + platinum) histology observed in KEYNOTE-671.

Second line

In the second line, given the relatively poor fitness of many patients by this stage a fixed proportion of 40% are assumed to receive best supportive care (BSC) irrespective of treatment arm or IO-eligibility status. Advice at the July 2022 Advisory Board supported a 30-40% range.(36) Second-line patients are assumed to receive no targeted treatments or IOs as all eligible patients will have received them in the first line and therefore the remaining 60% were divided evenly between docetaxel and platinum doublet chemotherapy.

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Table 45. Subsequent treatment market shares by IO eligibility status and peri-adjuvant treatment arm

	Cohort description	Peri-adjuvant pembrolizumab or Neoadjuvant nivolumab		Neoadjuvant chemotherapy	Surgery alone
First line:		**IO-eligible (1L)**	**IO-ineligible (1L)**	**IO-eligible (1L)**	**IO-eligible (1L)**
Osimertinib	Eligible for a TKI	15%	15%	15%	15%
Pembrolizumab + carboplatin + paclitaxel	PD-L1 <50%, Squamous	32.95%	0%	32.95%	33%
Pembrolizumab + pemetrexed + platinum (PDC)	PD-L1 <50%, Non-squamous	23.66%	0%	23.66%	24%
Pembrolizumab	PD-L1 ≥50%	22.71%	0%	22.71%	23%
Atezolizumab	PD-L1 ≥50%	5.68%	0%	5.68%	6%
Carboplatin + paclitaxel	Squamous	0%	49.47%	0.00%	0%
Pemetrexed + platinum (PDC)	Non-squamous	0%	35.53%	0.00%	0%
Second line:		**IO-eligible (2L)**	**IO-ineligible (2L)**	**IO-eligible (2L)**	**IO-eligible (2L)**
Docetaxel		30%	30%	30%	30%
Pemetrexed + platinum		30%	30%	30%	30%
No active treatment (BSC)		40%	40%	40%	40%

Abbreviations: 1L, first line; 2L, second line; BSC, best supportive care; IO, immunotherapy; PDC, platinum doublet chemotherapy.

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Estimation of mean survival by first-line treatment for metastatic NSCLC

As with the transitions starting from the LR/P state, the transition from DM to death was modelled using exponential distributions and time-constant HRs, as the memoryless property of Markov models prevents the use of transition probabilities that depend on time spent in an intermediate health state.

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

Five first-line treatment options were designated as reference treatments (Table 46): pembrolizumab + pemetrexed + platinum (for non-squamous NSCLC); pembrolizumab + carboplatin + paclitaxel (for squamous NSCLC); osimertinib (for EGFR+ [as a surrogate for mutation+] NSCLC); pembrolizumab (PD-L1 ≥50% NSCLC) and atezolizumab (for PD-L1 ≥50% NSCLC). Pembrolizumab monotherapy is reimbursed for PD-L1>50% and we used the subgroup from KEYNOTE-042 with PD-L1 ≥50% as the reference population. For each of these treatments, weekly exponential rates of OS and PFS failure were computed to match the median OS and PFS reported in the pivotal clinical trials of each treatment within the relevant indicated population. The resulting exponential models for OS and PFS alongside the observed Kaplan–Meier curves for the pembrolizumab regimens are presented in Appendix M.

For the remaining metastatic treatment regimens in first line, Pemetrexed + platinum (for non-squamous patients having chemotherapy) and Carboplatin + paclitaxel (for non-squamous patients having chemotherapy), HRs for OS and PFS versus the corresponding pembrolizumab reference treatment were obtained from within trial hazard ratios (Table 47).

Table 46. Exponential models of OS and PFS with reference treatments in the 1L metastatic NSCLC setting

Metastatic regimen (reference treatment)	Indicated population	Exponential weekly rate (SE)		Sources
		OS	PFS	
Pembrolizumab + pemetrexed + platinum (PDC)	Non-squamous NSCLC	0.0073 (0.0004)	0.0176 (0.0011)	KEYNOTE-189 data on file (data cut-off: 08 Mar 2022)
Pembrolizumab + carboplatin + paclitaxel	Squamous NSCLC	0.0093 (0.0008)	0.0198 (0.0017)	KEYNOTE-407 data on file (data cut-off: 23 Feb 2022)
Osimertinib	EGFR+ NSCLC (assumed efficacy for proportion on TKI)	0.0041 (0.0002)	0.0084 (0.0008)	Ramalingam et al. (2020) (101) & Soria et al. (2018) (102) [FLAURA]

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Metastatic regimen (reference treatment)	Indicated population	Exponential weekly rate (SE)		Sources
		OS	PFS	
Pembrolizumab	PD-L1 ≥ 50% NSCLC	0.0080 (0.0009)	0.0245 (0.0022)	KEYNOTE-042 data on file (data cut-off date: 28 May 2021)
Atezolizumab	PD-L1 ≥ 50% NSCLC	0.0079 (0.0009)	0.0197 (0.0023)	Herbst et al. (2020) (103) [IMpower110]

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; OS, overall survival; PDC, platinum doublet chemotherapy; PFS, progression-free survival; SE, standard error; TKI, tyrosine kinase inhibitor.

Table 47. HRs of OS and PFS with reference treatments in the 1L metastatic NSCLC setting

Metastatic regimen	Indicated population†	HR (SE) vs reference treatment		Sources
		Death (OS)	Death or progression (PFS)	
Pemetrexed + platinum (PDC)	Non-squamous NSCLC	1.67 (0.09)	2.00 (0.09)	KEYNOTE-189 (data cutoff date: 08 Mar 2022)
Carboplatin + (nab-)paclitaxel	Squamous NSCLC	1.41 (0.09)	1.61 (0.09)	KEYNOTE-407 data on file (data cut-off: 23 Feb 2022)

Abbreviations: HR, hazard ratio; NMA, network meta-analysis; NSCLC, non-small cell lung cancer; OS, overall survival; PDC, platinum doublet chemotherapy; PFS, progression-free survival; SE: standard error.
† Indicates the population in Table 46 that determines the reference treatment to which the HR is applied.

In each adjuvant arm, the probability of DM to death in each patient group was modelled to depend on a combination of both i) subsequent market shares of first-line treatments (as indicated in Table 45) and ii) the expected survival associated with each metastatic NSCLC treatment regimen (Table 46 and Table 47). Specifically, the weekly hazard of OS (starting from DM) was calculated in each adjuvant treatment arm as a weighted average of expected mean OS associated with different first-line treatments for metastatic NSCLC, based on the market shares of first-line advanced treatments in that arm. Expected PFS was similarly estimated for each adjuvant treatment arm based on the distributions of first-line treatments received, and the ratio of mean PFS to mean OS (calculated via area under the exponential survival curves) was estimated for each arm; this ratio was applied to relevant utility values to calculate overall utility values for use in the DM state, along with the weekly disease management costs within the DM state. An additional adjustment factor (1.0604) was applied to the DM→death OS hazard rates to account for potential differences between the patients in 1L DM NSCLC trials (used to model the DM state) and patients in the SEER

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Medicare database who had DM NSCLC after prior resection (who reflect the KEYNOTE-671 cohort). These overall weighted hazard rates are presented in Table 48.

Table 48. Hazards of death from DM health state

Model arm	Expected survival in DM state, weeks			Exponential weekly rate of DM→death	
	OS	PFS	Ratio PFS:OS	Based on OS	After applying adjustment factor†
Peri-adjuvant pembrolizumab (IO eligible)	140	60	0.43	0.0071	0.0076
Peri-adjuvant pembrolizumab (IO ineligible)	104	43	0.42	0.0097	0.0102
Neoadjuvant chemotherapy	140	60	0.43	0.0071	0.0076
Neoadjuvant nivolumab (IO eligible)	140	60	0.43	0.0071	0.0076
Neoadjuvant nivolumab (IO ineligible)	104	43	0.42	0.0097	0.0102
Surgery alone	140	60	0.43	0.0071	0.0076

Abbreviations: DM, distant metastases; IO, immunotherapy; OS, overall survival; PFS, progression-free survival.
† Adjustment factor of 1.0604 applied to account for potential differences between the patients in 1L DM NSCLC trials (used to model the DM state) and patients in the SEER Medicare database who had DM NSCLC after prior resection (who reflect the KEYNOTE-671 cohort) (OS hazard rate in SEER / OS hazard rate in current model = 0.00756 / 0.00713 = 1.0604).

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.

Scenario analysis using calibration of downstream transitions (from LR/P and DM) to observed OS

The model was initially developed to assume no ongoing benefit of peri-adjuvant pembrolizumab after recurrence or progression (i.e. the transition probabilities in the downstream health states were the same between model arms, other than differences resulting from different distributions of first-line treatments for DM NSCLC). It was not feasible to estimate different rates of LR/P→DM and LR/P→death for each model arm using SEER-Medicare data, as peri-adjuvant pembrolizumab was not yet an approved treatment strategy for NSCLC during the date range of the data (2007-2019). Peri-adjuvant pembrolizumab was therefore modelled to affect OS purely through its effect on EFS.

To validate this assumption, the fit of modelled OS versus the observed OS Kaplan-Meier curves in KEYNOTE-671 was examined (Figure 21). Compared with observed OS, the

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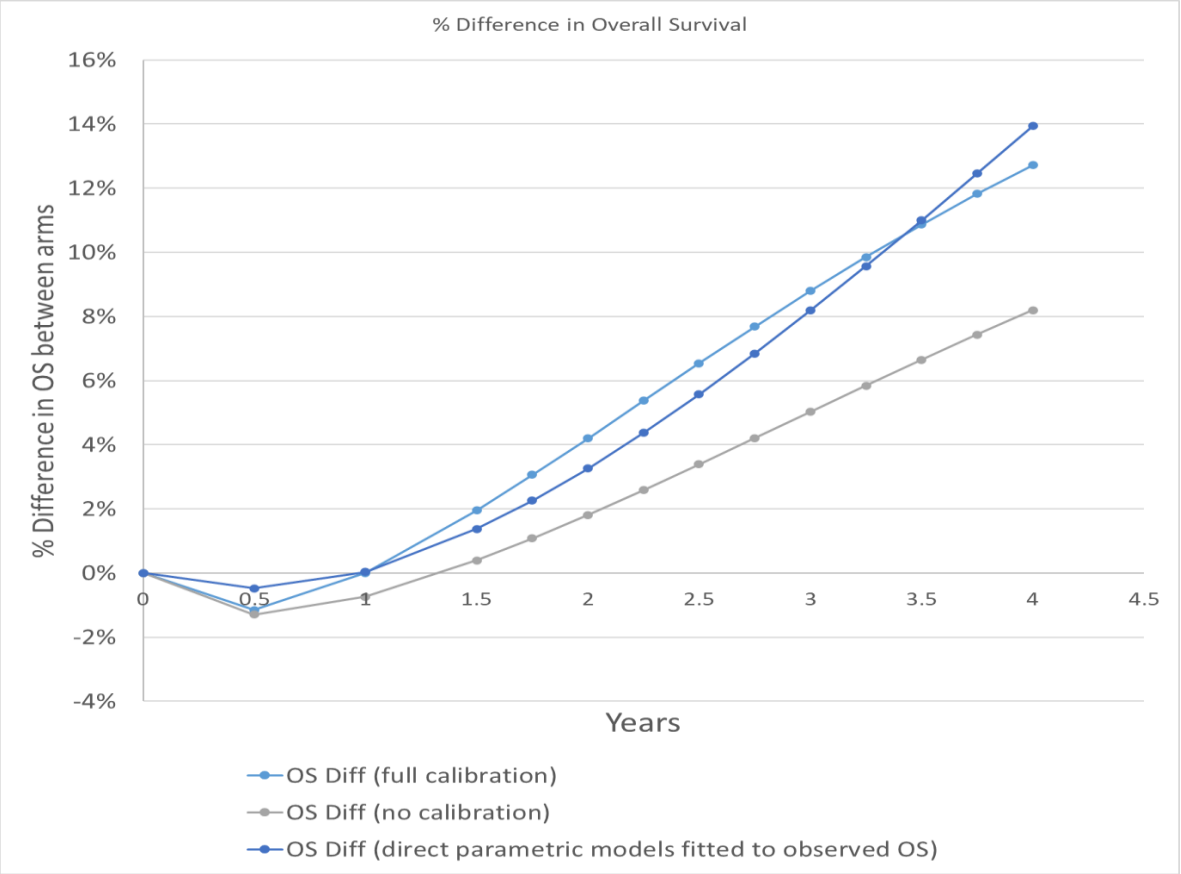
modelled OS curve was overpredicted in the neoadjuvant chemotherapy arm and (to a lesser extent) the pembrolizumab arm. The extent to which the model was able to predict the observed OS benefit associated with pembrolizumab was also examined and indicated that the OS benefit was somewhat underpredicted at all timepoints after six months (Figure 20).

Figure 20. Difference in OS with pembrolizumab versus neoadjuvant chemotherapy



Abbreviations: OS, overall survival.

The overall fit of the economic model to observed OS was adequate, which suggested that it characterised the natural history of resectable NSCLC reasonably well, but the greater level of overprediction in the chemotherapy arm suggested that one or more downstream arm-specific transition probabilities could be increased to achieve better fit to the observed OS. Because base-case EFS predictions in both arms aligned closely with observed EFS Kaplan-Meier curves from KEYNOTE-671 (Figure 16), the implication is that one or more of the post-recurrence transition probabilities (i.e., LR/P→DM, LR/P→death, or DM→death) should be lower in the pembrolizumab arm than in the control arm, at least temporarily, to enable the model to accurately predict the observed OS benefit accurately.

To explore the impact of this overprediction on the cost-effectiveness, a scenario analysis was conducted whereby the downstream transition probabilities were temporarily calibrated

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to achieve a better fit to observed OS in both treatment arms (see Appendix M.4 for details). Predicted versus observed OS before and after applying calibration are shown in Figure 21.

Figure 21. Predicted vs observed OS with base case selections, before/after calibration

A) Before calibration

B) After calibration

Abbreviation: OS, overall survival.

B.3.3.2. Adverse events

The model base-case includes all-cause grade 3+ adverse events (AEs) that occurred with a frequency of ≥5% in either arm of the KEYNOTE-671 trial (all-participants-as-treated population), or in the neoadjuvant nivolumab + chemotherapy arm of CheckMate-816. The CheckMate-816 study only captures AEs for 30 days after the last neoadjuvant dose, so do

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not capture chemotherapy-related adverse events for the 15% of patients in CheckMate-816 who received adjuvant chemotherapy. To account for this, AE risks for nivolumab were adjusted by adding an additional risk of 0.15 multiplied by the rate of each AE observed in the neoadjuvant chemotherapy arm of KEYNOTE-671. Adverse event rates in the “surgery alone arm were conservatively assumed to be zero. Mean duration per AE episode and mean number of episodes per patient with each included AE, pooled across treatment arms, were collected from KEYNOTE-671 and used within the model to estimate the duration of the disutility impact from each AE, regardless of treatment arm. This is conservative given that the impact of AEs would already be captured in the KEYNOTE-671 derived utilities applied for the health states as described in section B.3.4.1. The proportions of AEs resulting in hospitalisations were also collected from KEYNOTE-671 and were used to calculate the cost per AE episode in B.3.5.3. Utility decrements and costs are applied in the first cycle of the model (in-line with standard practice). These inputs are presented in Table 49.

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

AE type	AE risk (%), by treatment arm				Mean number of episodes per patient with AE	Mean duration of AE per episode (weeks)	% of AE episodes resulting in hospitalisation
	Pembro + chemo	Chemo	Nivolumab + chemo	Surgery			
Anaemia	9.8%	7.0%	3.9%	0.0%	1.0	46.7	15%
Neutropenia	0.3%	0.3%	8.6%	0.0%	1.0	2.1	50%
Neutrophil count decreased	21.7%	19.8%	10.3%	0.0%	1.4	5.4	4%
Platelet count decreased	5.3%	6.0%	0.9%	0.0%	1.3	11.0	27%
White blood cell count decreased	5.8%	5.5%	0.8%	0.0%	1.1	10.6	2%
Source:	*KEYNOTE-671 IA2*		*CheckMate-816 (45)*	*Assumption*	*KEYNOTE-671 IA2*		

Abbreviation: AE, adverse event.

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B.3.4. Measurement and valuation of health effects

As described in Appendix H, an SLR was conducted 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. Full details on the methodology and findings of the SLR, including search terms, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram and outcomes are detailed in Appendix H, and a summary is provided in B.3.4.3. The SLR did not identify any studies which provided HRQoL estimates for NSCLC during or after peri-adjuvant therapy. As such, the primary source of HRQoL values used in the model was the pivotal KEYNOTE-671 trial using the July 2023 data cut off. EQ-5D-5L utility values from KEYNOTE-671 were mapped to EQ-5D-3L using the mapping function developed by the Decision Support Unit (Hernández Alava et al. 2023),(69) and valued using the UK value set.

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

B.3.4.1.1. KEYNOTE-671

HRQoL was measured in KEYNOTE-671 using the EORTC-QLQ-C30 instrument and the EuroQoL EQ-5D-5L instrument. The NICE STA guidelines state that the EQ-5D is the preferred tool to measure HRQoL and that the economic model should consider HRQoL data collected directly from patients in the relevant clinical study to inform the utility weights, therefore the EQ-5D trial data were analysed for use in the economic evaluation.(70)

EQ-5D-5L was administered prior to dosing at Cycle 1 and Cycle 4 (week 11) during the neoadjuvant phase, and then at Cycles 1, 2, 3, 4, 7, 10 and 13 (i.e. week 1, 4, 7, 10, 19 28 and 37) during adjuvant treatment. They were also administered at the end of treatment visit, the 30-day safety follow-up and at post-treatment follow-up visits (every 16 weeks in years 2-3, and every six months in years 4-5).

Aligned with the economic model, utility values were calculated for the following health states:

- Event-free
- Local-regional recurrence or progression
- Distant metastases

Each EQ-5D response from KEYNOTE-671 was categorised into one of these health states (based on a determination of the patient's health state at the time of collection of each response) and included in the utility analysis accordingly.

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Utility values were estimated via descriptive analyses (see Appendix N.2) of patient-level EQ-5D-5L data from the IA2 data cut (10 July 2023) of KEYNOTE-671 and consisted of the full analysis set (FAS), defined as participants who have at least one EQ-5D assessment available and have received at least one dose of study medication. Compliance to the EQ-5D assessments was very good and remained over [redacted] for all timepoints in both treatment arms (see Appendix N). Summary statistics were computed based on multiple records per participant, which were treated as independent observations. Baseline measurements were excluded from the analysis, in addition to any patient-visits with missing or incomplete EQ-5D-5L responses. The analyses were pooled across treatment arms to estimate the average utility for all patients in the trial, as there was no clinically meaningful difference observed between the treatment arms in either the neoadjuvant or adjuvant phases of the KEYNOTE-671 trial. To align with NICE's position statement for reference case analyses, the EQ-5D-5L measurements collected in KEYNOTE-671 were mapped to the EQ-5D-3L tool using the crosswalk algorithm developed by the NICE Decision Support Unit.(Hernández Alava et al. 2023) (69)

It was not possible to generate utility values for pre- versus post-progression in the DM health state as the available follow-up data from KEYNOTE-671 to date were too limited to capture the average utility over the entire post-progression disease course until death. The utility value for the DM state from KEYNOTE-671 may therefore be used as an approximation of utility in the pre-progression DM sub-state only.

Health state utility values derived from the trial are presented below in Table 50.

Table 50. Health state utilities derived from KEYNOTE-671

Health state	Patients, n	Records, n	EQ-5D-3L		Source
			Value	SE	
Event-free	[redacted]	[redacted]	[redacted]	[redacted]	KEYNOTE-671 IA2 (data cut-off 10 July 2023)
Event-free (without any AEs)	[redacted]	[redacted]	0.882	0.004	
Event-free (without grade 3+ AEs)	[redacted]	[redacted]	0.830	0.002	
Event-free (with grade 3+ AEs)	[redacted]	[redacted]	0.791	0.007	
Local-regional recurrence	[redacted]	[redacted]	0.776	0.017	
Distant metastases (pre-progression)	[redacted]	[redacted]	0.727	0.019	

Abbreviations: AE: Adverse events; SE, standard error.

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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. Therefore, the EQ-5D-5L measurements collected in KEYNOTE-671 were mapped to the EQ-5D-3L tool using the mapping function developed by the Decision Support Unit,(Hernández Alava et al. 2023) (69) as recommended in the NICE methods guide. The EQ-5D-3L UK value set, developed based on the time trade-off method, was then used to derive utility values for the economic model.(104)

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

The SLR described in Appendix H was conducted to identify studies reporting utility values for patients receiving neoadjuvant, peri-adjuvant or adjuvant treatment for NSCLC. Four studies were identified: one considered the neoadjuvant setting, two considered the adjuvant setting, and one looked at lung cancer patients across different stages and treatment strategies.

In the neoadjuvant setting, Felip et al, 2022 reported UK-weighted EQ-5D-3L utility data from the CheckMate 816 trial, but results are reported only as change from baseline over time rather than as health state utilities.(105) In the adjuvant setting, the LuCaBIS study(Andreas et al, 2018 (106)) reported EQ-5D utility values for European patients, but methodological details are sparse (such that it is not clear which value set was used to obtain utility weights), the response rate was relatively poor (58%) and the sample size for LR and DM states was very small (n=19 and n=32, respectively). These limitations may partly explain why the reported utility for the DM state is higher than for the LR state. Leiter et al, 2022 reports only disutilities for comorbidities in NSCLC and therefore does not provide useful information for the current decision problem;(107) and Tramontano et al, 2015 reports EQ-5D utility values for lung cancer patients by disease stage and across a wide mix of different treatment strategies, however these are weighted using the US value set which is not aligned with the NICE reference case.(108)

In addition, the SLR described in Appendix H identified six UK-based economic evaluations: one in the neoadjuvant setting (NICE TA876, based on CheckMate 816 [neoadjuvant nivolumab + chemotherapy](7)) and five in the adjuvant setting (NICE TA761(5) and SMC2383, based on ADAURA [adjuvant osimertinib]; NICE TA823(6), SMC2492 and Yip et al, 2023(109) [adjuvant atezolizumab]).

The actual trial utilities from CheckMate 816 were redacted in TA823 therefore cannot be considered for the current appraisal. Utilities in the osimertinib models (NICE TA761, SMC2383) were obtained by mapping SF-36 values from ADAURA to EQ-5D-3L; whilst

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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 locoregional recurrence (LRR) states in the absence of reliable HRQoL data for the LRR 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)(21) and a study by Labbé et al, 2017, respectively.(5, 21, 65) 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 these sources did not all fully align with the NICE reference case (e.g. Jang et al, 2010(66) and Van den Hout et al, 2006(68) used non-UK value sets).(6, 109)

A summary of the HRQoL sources identified via the SLR is provided in Appendix H.2.5.

B.3.4.4. Adverse reactions

AE-related disutility was applied as a one-time QALY decrement in the first model cycle. This disutility associated with AEs was calculated in each treatment arm as a function of treatment-specific AE risks; the mean duration per AE episode; the mean number of episodes per affected patient in KEYNOTE-671; and the estimated disutility associated with an active grade 3+ AE. This disutility of an active grade 3+ AE was calculated as the difference between the mean utility for “EF with grade 3+ AE” minus the mean utility for “EF without any AE”, as estimated from KEYNOTE-671 (Table 51).

Inputs and assumptions related to AE incidence, duration and number of episodes are described in section B.3.3.2.

Table 51. Estimated AE disutility for grade 3+ AEs, derived from KEYNOTE-671

Health state	Patients, n	Records, n	EQ-5D-3L		Source
			Mean	SE	
EF (without any AEs)	[redacted]	[redacted]	0.882	0.004	KEYNOTE-671 (data cut-off 10 July 2023)
EF (with grade 3+ AEs)	[redacted]	[redacted]	0.791	0.007	
Disutility for grade 3+ AEs†	-	-	-0.091	0.016	

Abbreviations: AE, adverse event; SE, standard error.

† Calculated as the difference between the mean utility across patient-visits in the event-free state with any grade 3+ AE minus the mean utility in the disease-free state with no grade 3+ AE.

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

As stated in the NICE methods guide, the preferred approach for incorporating HRQoL into the economic model is to collect health state measurements from patients relevant to the decision problem using the EQ-5D-3L tool, and the utility weights should be elicited from the UK general population (70). Accordingly, for the EF, LR/P, and pre-progression DM health states the base case analysis used utility values derived from the analyses of patient-level EQ-5D-5L data collected from the KEYNOTE-671 trial. The EQ-5D-5L measurements were mapped back to the EQ-5D-3L version of the tool using the NICE DSU algorithm(69) and utilities derived using the UK value set.(104) A disutility for AEs was also estimated from the KEYNOTE-671 trial and applied as a one-off decrement in the first model cycle (Table 52).

For the EF health state, the “EF without any AEs” utility value was selected for the base case to best reflect the utility of the health state over the whole model time horizon. This was chosen because cured patients may survive for decades in this health state (the mean undiscounted LYs in the control arm of the base case economic model was >7) but most EQ-5D forms were completed during the first year of the trial. Overall EF utilities from the trial are therefore likely to be influenced by AEs related to the systemic and radical treatments they had received during this first year and therefore underestimate the true utility for the EF health state over the complete time horizon. The other utility options were retained for scenario analyses. This approach was in line with NICE TA837.(77)

In line with the model structure, the DM health state was comprised of two sub-states (pre-progression and post-progression) to capture differences in outcomes and costs of patients who develop advanced disease. As discussed in B.3.4.1, EQ-5D data corresponding to post-progression were not available from KEYNOTE-671 as the available follow-up from the trial was too limited to enable a robust analysis of post-progression utility. Alternate sources were therefore reviewed for suitability to inform this parameter.

All studies identified via the SLR had limitations regarding methodology, alignment with the NICE reference case, or relevance to the population in the current decision problem (see section B.3.4.3). Consequently, utility values were instead obtained from analysis of the EQ-5D data collected in recent RCTs of pembrolizumab for untreated NSCLC: KEYNOTE-189 (non-squamous NSCLC, data-cut 8 March 2022) and KEYNOTE-407 (squamous NSCLC, data-cut 23 February 2022). For each trial, the pooled average utility value across patient-visits within the post-progression DM state was estimated and valued using the UK value set.(104) An overall utility for the post-progression DM state was then calculated by

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weighting each trial by the corresponding proportion of patients with squamous or non-squamous histology in KEYNOTE-671. Finally, in each adjuvant treatment arm, utility in the whole DM state was then 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- versus post-progression within the distant metastases state (given the mix of first-line metastatic treatments received and the efficacy of those treatments) (see Table 48).

A summary of the utilities used in the base case analysis is provided in Table 52.

Table 52. Summary of utility values for cost-effectiveness analysis

State	Utility, mean	SE†	Reference in submission	Source and justification
EF (without AEs)	0.882	0.008	B.3.4.1, p138	EQ-5D-3L values derived from patients directly relevant to the decision problem (from KEYNOTE-671) using UK value set, in line with the NICE reference case
LR/P	0.776	0.034		
DM (pre-progression)	0.727	0.038		
DM (post-progression)	0.657	0.030		KEYNOTE-407, 23 February 2022 % Squamous, KEYNOTE-671: 43.2%
	0.679	0.026		KEYNOTE-189, 8 March 2023 % Non-squamous, KEYNOTE-671: 56.8%
Grade 3+ AE	-0.091	0.016	B.3.4.4, p140	KEYNOTE-671, in line with the NICE reference case

Abbreviations: AE, adverse event; SE, standard error.
† SE from utility analysis doubled to account for repeated measures.

B.3.4.5.1. Age-related disutility

Within the model, age adjustment was applied to account for the deterioration in utility as patients age. Age-related disutility was based on the formula from Ara and Brazier which uses a linear regression model to predict the mean utility for the general population, conditional based on age, age squared and sex (Table 53).(110) This was applied within the model by use of the baseline age (63.1 years) and proportion female (29.4%).

Table 53. Regression coefficients used to estimate age-related disutility

Variable	Coefficient	Source
Age (years)	-0.0002587	Ara and Brazier, 2010 (110)
Age^2	-0.0000332	
Male	0.0212126	

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Variable	Coefficient	Source
Intercept	0.9508566	

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

An SLR was conducted to identify healthcare resource use and direct and indirect costs associated with peri-adjuvant treatment of NSCLC. All relevant search strategies, search identification, and methodology are presented in Appendix I.

In line with the NICE reference case, the model took a UK National Health Service (NHS) and Personal Social Services (PSS) perspective and therefore only direct healthcare costs related to the treatment and management of NSCLC were considered.(70) Evidence on resources used by patients in the treatment pathway were sourced from the KEYNOTE-671 trial and the published literature. Healthcare costs were obtained from publicly available sources which primarily included the British National Formulary (BNF),(111) NHS Reference Costs, (112) and the Personal Social Services Research Unit (PSSRU)(113) to ensure the model used the most up to date costs relevant to UK practice. These were supplemented by costs from published studies where relevant inputs from the public sources were not available. All costs are reported in 2022 GBP.

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

The pembrolizumab (plus chemotherapy) dose is consistent with the license (for SmPC see Appendix C). In the neoadjuvant setting, pembrolizumab is administered at 200 mg every 3 weeks (Q3W) for 4 cycles. As discussed in section B.3.2.1, clinical advice indicated that clinicians would prefer to use a Q6W dosing regimen where pembrolizumab is offered less frequently at double the dose in the adjuvant phase, therefore this assumption is used in the base case. It is assumed that the first dose in this setting will be 200 mg with the first 400 mg dose administered 3 weeks later. This allows patients to be monitored as they reinitiate treatment with pembrolizumab. The Q3W dosing schedule used in the adjuvant phase of the trial is explored in scenario analyses. The dosing regimens applied for pembrolizumab and comparator arms are shown in Table 54.

Table 54. Neoadjuvant regimens dosing schedule

Regimen	Component	Dosing schedule description	% receiving component
Peri-adjuvant pembrolizumab	Pembrolizumab (neoadjuvant)	200 mg IV Q3W, 4 cycles	100%

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Regimen	Component	Dosing schedule description	% receiving component
(KEYNOTE-671)(114)	Cisplatin (neoadjuvant)	75 mg/m^2 IV Q3W, 4 cycles	100%
	Gemcitabine (neoadjuvant)	1000 mg/m^2 IV on days 1 and 8 of 3- week cycles (squamous tumours only)	43.9%
	Pemetrexed (neoadjuvant)	500 mg/m^2 IV Q3W (non-squamous tumours only)	56.1%
	Pembrolizumab (adjuvant)	200 mg IV for first cycle then 400 mg IV Q6W, up to 6 cycles (base case) OR 200 mg IV Q3W, up to 13 cycles (scenario)	73.2%†
Neoadjuvant chemotherapy (KEYNOTE-671)(114)	Cisplatin	75 mg/m2 IV Q3W up to 4 cycles	100.0%
	Gemcitabine	1000 mg/m2 IV on days 1 and 8 Q3W up to 4 cycles	43.9%
	Pemetrexed	500 mg/m2 IV Q3W up to 4 cycles,	56.1%
Neoadjuvant nivolumab (CheckMate-816)(45)	Nivolumab	360 mg IV Q3W up to 3 cycles	100.0%
	Carboplatin	AUC 5 or 6 mg/ml/min IV Q3W up to 3 cycles	42.3%
	Cisplatin	75 mg/m2 IV Q3W up to 3 cycles	57.7%
	Gemcitabine	1000 or 1250 mg/m2 IV on days 1 and 8 Q3W up to 3 cycles	27.3%
	Paclitaxel	175 or 200 mg/m2 IV Q3W up to 3 cycles	27.3%
	Pemetrexed	500 mg/m2 IV Q3W up to 3 cycles	45.5%
Surgery alone	N/A	N/A	N/A

Abbreviations: AUC, area under the curve; IV, Intravenous; N/A, not applicable; QxW, every x weeks.
Source: KEYNOTE-671 (July 2023 data cut-off)
† Reflects patients starting adjuvant therapy after surgery – see section B.3.5.1.1 for details.

Unit drug costs for pembrolizumab, chemotherapy, comparator regimens and subsequent treatments are summarised in Table 55, and in more detail in Appendix K. 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).(111, 115) A PAS with a simple discount is currently in place for pembrolizumab, reported in Appendix K.

Table 55. Unit drug costs for treatments in the neoadjuvant, adjuvant, LR/P, and/or DM settings

Regimen or component	Strength per vial or pack (mg)	Pack size	List price per vial or pack (£)
Atezolizumab	1,200	1	£3,807.69*
Carboplatin	450	1	£14.69
Cisplatin	50	1	£5.58
Docetaxel	160	1	£16.04
Gemcitabine	200	1	£4.13

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Nivolumab	40	1	£439.00*
Osimertinib	80	30	£5,385*
Paclitaxel	300	1	£17.40
Pembrolizumab	100	1	£2,630.00
Pemetrexed	100	1	£71.43
Vinorelbine	50	10	£158.63

Abbreviations: DM, distant metastases; LR/P, locoregional recurrence or progression.
Sources: BNF (111); eMIT national database (July 2022-June 2023) (115)
*MSD do not know the PAS prices of atezolizumab, nivolumab and osimertinib so are arbitrarily assuming they each have a 60% discount in all our analyses. This can be corrected by the EAG at a later date.

The cost of administration for all regimens is sourced from the NHS Reference Costs 2021/22. The SB13Z HRG code is used for pembrolizumab and nivolumab in the neoadjuvant phase (where administered in combination with chemotherapy) and SB12Z HRG code in the adjuvant phase (where pembrolizuamb is administered as monotherapy).(112) This is in line with the approach advised by the Cancer Drugs Fund lead in a recent pembrolizumab submission.(116) These costs, as well as administration costs for treatment regimens in the DM health state, are presented in Table 56.

Table 56. Administration costs

Regimen	Unit cost per administration	Source(112)
Neoadjuvant/adjuvant setting		
Pembrolizumab (or nivolumab) in combination with chemotherapy (neoadjuvant phase)	£354	2021/22 NHS Reference Cost, SB13Z: Deliver Complex Parenteral Chemotherapy at First Attendance
Pembrolizumab monotherapy (adjuvant phase)	£287	2021/22 NHS Reference Cost, SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance
Neoadjuvant chemotherapy	£354	2021/22 NHS Reference Cost, SB13Z: Deliver Complex Parenteral Chemotherapy at First Attendance
DM state		
IO monotherapy or Single agent chemotherapy	£287	2021/22 NHS Reference Cost, SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance
Combination chemotherapy (± pembrolizumab)	£354	2021/22 NHS Reference Cost, SB13Z: Deliver Complex Parenteral Chemotherapy at First Attendance

Abbreviations: DM, distant metastases; NHS, National Health Service.

B.3.5.1.1. Time on treatment

Time on treatment (ToT) for each drug component of the peri-adjuvant pembrolizumab and neoadjuvant chemotherapy regimens was based on the observed proportions of patients

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who received each scheduled cycle in each arm of KEYNOTE-671 (Table 57). No patient remained on neoadjuvant or adjuvant treatment in KEYNOTE-671 as of the data cutoff date; therefore, the observed proportions of patients who received each neoadjuvant/adjuvant treatment cycle could be used directly, without the need for extrapolation beyond the observed trial period. In the trial, patients could receive 4 doses of neoadjuvant therapy and (in the pembrolizumab arm) up to 13 doses of adjuvant pembrolizumab corresponding to a maximum of 17 doses of pembrolizumab. Within the model, the costs of treatment were applied at fixed intervals of every 3 weeks (Q3W) starting with the first neoadjuvant infusion at cycle 0. In the pembrolizumab arm, the first dose of adjuvant treatment was applied at week 24, accounting for the treatment-free period pre- and post-surgery observed in KEYNOTE-671 (Table 58).

Treatment duration for neoadjuvant nivolumab was based on reported ToT statistics reported in the pivotal trial publication for CheckMate 816. A weekly exponential rate of discontinuation was calculated based on 93.8% of patients completing 3 doses of Q3W neoadjuvant nivolumab + chemotherapy over a six week period (-ln(0.938/6) = 0.0107).(45)

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Table 57. Proportion of patients receiving each cycle of treatment in the model, as observed in KEYNOTE-671

Treatment cycle number		Weeks from model start	% of patients who received each cycle of each drug component, among those assigned to receive it							
			Peri-adjuvant pembrolizumab					*Neoadjuvant chemotherapy*		
			Pembrolizumab	*Pembrolizumab (non-pCR-only scenario)†*	*Cisplatin*	*Gemcitabine*	*Pemetrexed*	*Cisplatin*	*Gemcitabine*	*Pemetrexed*
% assigned			**100%**	**100%**	**100%**	**43.9%**	**56.1%**	**100%**	**43.9%**	**56.1%**
Neoadjuvant	1	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% receiving adjuvant			***73.2%***	[redacted]	-	-	-	-	-	-
Adjuvant	1	24‡	[redacted]	[redacted]	-	-	-	-	-	-
	2	27	[redacted]	[redacted]	-	-	-	-	-	-
	3	30	[redacted]	[redacted]	-	-	-	-	-	-
	4	33	[redacted]	[redacted]	-	-	-	-	-	-
	5	36	[redacted]	[redacted]	-	-	-	-	-	-
	6	39	[redacted]	[redacted]	-	-	-	-	-	-
	7	42	[redacted]	[redacted]	-	-	-	-	-	-
	8	45	[redacted]	[redacted]	-	-	-	-	-	-
	9	48	[redacted]	[redacted]	-	-	-	-	-	-
	10	51	[redacted]	[redacted]	-	-	-	-	-	-
	11	54	[redacted]	[redacted]	-	-	-	-	-	-
	12	57	[redacted]	[redacted]	-	-	-	-	-	-
	13	60	[redacted]	[redacted]	-	-	-	-	-	-

Abbreviations: pCR, pathological complete response.

† In this scenario analysis, adjuvant pembrolizumab is assumed to only be given to patients who do not achieve a pCR after neoadjuvant treatment – the proportion receiving adjuvant pembrolizumab is therefore the proportion not achieving pCR (81.9%) multiplied by the proportion of non-pCR patients who start adjuvant therapy (68.6%) = 56.2%.

‡ Accounts for treatment-free period pre- and post-surgery, as observed in KEYNOTE-671 (Table 58).

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Table 58. Treatment-free period pre- and post-surgery in pembrolizumab arm (KEYNOTE-671)

	Observed in KEYNOTE-671, mean	
	Days	Weeks
Time from last neoadjuvant dose to surgery	[redacted]	[redacted]
Time from surgery to first adjuvant dose	[redacted]	[redacted]

B.3.5.2. Health-state unit costs and resource use

B.3.5.2.1. Overview of health state costs

The total per cycle costs for patients in the EF, LR/P and DM health states are summarised in Table 59 and Table 60. 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 modifications from our 2023 Clinical Advisory Board.(5, 6, 71) 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 validation by UK oncologists. In the osimertinib appraisal, the resource use estimates were originally based on both the Andreas et al, 2018 study and NICE TA654 appraisal.(21, 106) Resource use estimates from both appraisals were discussed with clinical experts from MSD's 2023 Clinical Advisory Board. The experts generally preferred the approach from the atezolizumab appraisal except for hospitalisations, which were not costed in the atezolizumab appraisal, and the experts confirmed that hospitalisations would occur at broadly the frequency presented in the osimertinib appraisal. The exception to this was that the clinical experts considered the hospitalisation resource use in the EF health state to be 1 event every 2 years (instead of 0.9 per year originally).(71) Therefore, in the model this value was set to 0.5 events per year. This, and all other resource use estimates from the atezolizumab appraisal, were subsequently converted into a weekly resource use rate in keeping with the weekly cycle length in the model.

Consistent with the TA823 approach,(6) patients in either treatment arm receive the same total weekly health state cost. As there is a single DM health state in the model, resource use estimates from the atezolizumab appraisal were weighted by the estimated time patients spend in pre-progression and post-progression DM states in each arm. This was determined by the modeled distribution of first line market shares and the resulting ratio of PFS:OS (Table 48; PFS:OS ratios = 0.42−0.43). 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 and PSSRU (2022).(112, 113)

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As in the previous appraisals, a one-time cost was also applied to all patients transitioning into the DM state from any other state. 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.(71)

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Table 59. Healthcare resource use by EF and LR/P health states

Resource use element	Unit cost	EF years 0-7		EF years 5-7		EF years 7+		LR/P		Reference
		%	# per week	%	# per week	%	# per week	%	# per week	
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)(5, 71, 112)
Outpatient visit	£206	100%	0.027	53%	0.027	5%	0.027	100%	0.091	Per visit. NHS Reference Costs 2021-22: Code 370 outpatient medical oncology(112)
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(113)
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).(113)
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.(113)
Therapist visit	£50	100%	0	53%	0	5%	0	100%	0	PSSRU 2022 cost per hour for community occupational therapist (including qualifications)(113)
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)(112)
Chest radiography	£38	100%	0.027	53%	0.027	5%	0.027	100%	0.023	Per visit. NHS Reference Costs 2021-22: DPAF(112)

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Electrocardio-gram	£181	100%	0	53%	0	5%	0	100%	0	NHS Reference Costs 2021-22, Electrocardiogram Monitoring or Stress Testing, EY51Z(112)
Resource use cost per week cost		**£41.66**		**£21.87**		**£2.08**		**£133.25**		**Calculation (weighted average)**

Abbreviations: CT, computed tomography; DFs, disease-free survival; EF, event-free; GP, general practitioner; LR/P, locoregional recurrence or progression; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.
Source: NICE TA823.(6)

Table 60 Healthcare resource use by DM (pre-progression and post progression)

Resource use element	Unit cost	DM (pre-progression) One-time		DM (pre-progression)		DM (post-progression)		Reference
		%	#	%	# per week	%	# per week	
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)(5, 71, 112)
Outpatient visit	£206	100%	0.18	100%	0.18	100%	0.15	Per visit. NHS Reference Costs 2021-22: Code 370 outpatient medical oncology(112)
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(113)
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)(113)
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.(113)
Therapist visit	£50	100%	0	100%	0	100%	0.50	PSSRU 2022 cost per hour for community occupational therapist (including qualifications)(113)

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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)(112)
Chest radiography	£38	100%	0.13	100%	0.13	100%	0.12	Per visit. NHS Reference Costs 2021-22: DPAF(112)
Electrocardiogram	£181	100%	0.02	100%	0.02	100%	0.02	NHS Reference Costs 2021-22, Electrocardiogram Monitoring or Stress Testing, EY51Z(112)
PET-CT scan	£722	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)(112)
MRI	£322	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)(112)
Resource use		**£1,299 one-time**		**£254 per week**		**£312 per week**		**Calculation (weighted average)**

Abbreviations: CT, computed tomography; DFS, disease-free survival; DM, distant metastases; GP, general practitioner; LR/P, locoregional recurrence or progression; NHS, National Health Service; PET, positron emission tomography; PSSRU, Personal Social Services Research Unit.
Source: NICE TA823.(6)

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B.3.5.2.2. Event-free health state costs

One-off costs were applied in the EF health state to account for the costs of initial surgery and of adjuvant radiotherapy following surgery, with the approach summarised in Table 61. Costs were calculated based on the observed proportions of patients who underwent surgery as planned and who received post-surgery radiotherapy in KEYNOTE-671 and CheckMate-816. The timing of the costs was based on the mean time from the final neoadjuvant to dose to surgery and the mean time from surgery to the initiation of adjuvant radiotherapy based on the clinical trials. The costs applied for surgery and radiotherapy are summarised in Table 62.

Table 61. Proportion of patients receiving surgery and radiotherapy in the EF state

Resource use element	Pembrolizumab (KN-671)	Chemotherapy (KN-671)	Nivolumab (CM-816)	Surgery
Surgery				
% of patients receiving	82.1%	79.4%	83.2%	100%
Week of last neoadjuvant dose	9	9	6	N/A
Mean weeks from last neoadjuvant dose to surgery	[redacted]	[redacted]	[redacted]	N/A
Apply surgery cost at the following week	[redacted]	[redacted]	[redacted]	[redacted]
Adjuvant Radiotherapy				
% of patients receiving	8.8%	13.0%	8.0%	13.0%†
Mean weeks from surgery to adjuvant radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Apply radiotherapy cost at the following week	[redacted]	[redacted]	[redacted]	[redacted]

† Proportion of patients in surgery alone arm receiving adjuvant radiotherapy and time from surgery to adjuvant radiotherapy were assumed to be equal to the KEYNOTE-671 control arm.
‡ Time from surgery to radiotherapy was not reported in CheckMate-816 and was assumed to be equal to the pembrolizumab arm in KEYNOTE-671.

Table 62. Unit costs of one-off costs in the EF health state

Resource	Unit cost	Notes and unit cost source
Surgery	£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) (112)
Radiotherapy	£5,557*	NHS Reference costs 2021/22, replicating the costing approach used in NG122 (weighted average of continuous hyperfractionated accelerated radiotherapy,

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		hyperfractionated accelerated radiotherapy, and standard fractionated radiotherapy) (see B.3.5.4.1) (3, 112)

Abbreviations: NHS, National Health Service.

B.3.5.2.3. Locoregional recurrence or progression health state costs

In addition to the total health state costs per cycle, patients receive a one-time treatment cost related to local-regional recurrence of their cancer on entry into the LR/P state as summarised in Table 63. 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.(36) Clinicians also advised that in UK practice some patients would get durvalumab after chemo-radiotherapy. This was excluded from the economic model for several reasons: it would only relate to a specific subset of patients (unresectable stage III PD-L1≥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. Although this is noted as a limitation of the model, given that it only applies to a subset of patients and that the committee's preferred scenarios in the FAD for TA798(4) were "between £20,000 and £30,000/QALY" (and thus the implied additional Net Health Benefit is small), excluding it is unlikely to meaningfully bias the analysis.

Table 63. One-time treatment costs in the LR/P health state

Resource element in LR/P state	% of patients(36)	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)(112)
Radiotherapy (CRT)	30%	£5,557	NHS Reference costs 2021/22, replicating the costing approach used in NG122 (weighted average of continuous hyper-fractionated accelerated radiotherapy, hyper-fractionated accelerated radiotherapy, and standard fractionated radiotherapy) (see B.3.5.4.1)(3, 112)
Radiotherapy (alone)	20%		
Systemic therapy (chemotherapy alone).	30%	£1,977	Costed as vinorelbine + cisplatin (5.3 weeks treatment in KN671). 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/P: local-regional recurrence or progression; RT: radiotherapy.

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B.3.5.2.4. Subsequent treatment costs in the distant metastases 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 DM state. Patients who entered the DM 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 IO eligibility status as fully described in B.3.3.1.3. As also described in B.3.3.1.3, subsequent treatment market shares for second-line metastatic treatment were assumed to be the same irrespective of IO eligibility or original adjuvant treatment received.

The drug acquisition cost per administration is based on unit drug costs (as already summarised in Table 55) and defined dosing schedules as shown in Table 64. The dosing schedules and stopping rules were based on prescribing information and the design of the pivotal trials. Administration costs were applied as outlined in Table 56. For simplicity, consistency and dynamism within the model, times on treatment were assumed to be equal to exponential rate of PFS failure on the drug as derived within the model, subject to a maximum treatment duration based on recommended dosing schedules (see section B.3.5.2.5).

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Table 64. 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)
Carboplatin + (nab-)paclitaxel (SQ)	Carboplatin	AUC 6 mg/ml/min IV Q3W, up to 4 cycles	12	100.0%	Paz-Ares et al. (2018) [KEYNOTE-407] (1L trial)(117)
	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) [KEYNOTE-407] (1L trial)(117)
	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) & Gadgeel et al. (2020) [KEYNOTE-189](118, 119)
	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 +	Pemetrexed	500 mg/m2 IV Q3W	No max	100.0%	

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platinum	Carboplatin	AUC 5 mg/ml/min IV Q3W, up to 4 cycles	12	71.8%	Gandhi et al. (2018) & Gadgeel et al. (2020) [KEYNOTE-189](118, 119)
	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); Fossella et al. (2000) [TAX 320](120)
Pemetrexed + platinum	Pemetrexed	500 mg/m2 IV Q3W	No max	100.0%	Gandhi et al. (2018) & Gadgeel et al. (2020) [KEYNOTE-189](118, 119)
	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: AUC, area under the curve; IV, intravenous; NSCLC, non-small cell lung cancer; NSQ, non-squamous; Q#W, once every # weeks; SQ, squamous; ToT, time on treatment.

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B.3.5.2.5. 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 46. For second-line treatments, mean treatment durations were based on empirical estimates from 9,121 patients from the Flatiron database.(121) This cohort comprised of adult patients with metastatic NSCLC who initiated second-line treatment, as summarised in Table 65. This cohort comprised adults who were previously treated with first-line systemic anti-cancer therapy (IO monotherapy, IO combination, chemotherapy, and/or TKIs) 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 O.

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 65. Time on treatment for second-line treatment regimens

Second-line treatment regimen	Component	Mean ToT, weeks
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 O for methodology).

B.3.5.3. Adverse reaction unit costs and resource use

The costs of grade 3+ with ≥5% frequency in pembrolizumab and placebo are summarised in Table 66. As outlined in B.3.3.2 and in line with previous NICE appraisals, costs associated with AEs were applied as a one-off cost 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 and mean cost per episode of the AE (adjusting for proportions with and without hospitalisations) (Table 49). 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, a unit cost of £160 was applied which

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is the cost of a clinical oncology outpatient attendance (code 800) in the NHS reference costs 2021/22.(112)

Table 66. Cost per grade 3+ adverse event

Grade 3-5 AEs	Cost per event (with hospitalisation)	Source(112)
Anaemia	£941.32	NHS Reference Cost 2021/22, SA03G, SA03H, SA04G, SA04H, SA04J, SA04K, SA04L, SA05G, SA05H, SA05J, SA08G, SA08H, SA08J (weighted average)
Neutropenia	£1,365.64	NHS Reference Cost 2021/22, SA08G, SA08H, SA08J (weighted average) Costs for "Other Haematological or Splenic Disorders" - no specific costs for neutropenia
Neutrophil count reduced	£1,365.64	Assumed same costs as neutropenia
Platelet count decreased	£993.35	NHS Reference Cost 2021/22, SA12G, SA12H, SA12J, SA12K (weighted average of costs for thrombocytopenia)
White blood cell count decreased	£1,365.64	NHS Reference Cost 2021/22, SA08G, SA08H, SA08J (weighted average) Costs for "Other Haematological or Splenic Disorders" - no specific costs for leukopenia.

B.3.5.4. Miscellaneous unit costs and resource use

B.3.5.4.1. Radiotherapy costs

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 67. 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.(3) 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 LR/P health state, which was informed by the 2022 Clinical Advisory Board.(36) As summarised in Table 63, 30% of patients receive CRT and 20% receive radiotherapy. This remaining 20% was divided 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.(3, 112)

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Table 67. Average Cost of Radiotherapy

Resource use	Units	Cost	Source(3, 112)
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 NG122
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 NG122
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 NG122
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 NG122
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 NG122
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 NG122
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 NG122
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 NG122
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 NG122
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(36)

Abbreviations: CHART, continuous hyper fractionated accelerated radiotherapy; NHS, National Health Service.

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B.3.5.4.2. 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,(122) which has been used in several pembrolizumab appraisals and accepted by the NICE committee.(76-78, 123, 124)

B.3.5.4.3. pCR testing costs

Feedback from clinical advisors indicated that testing for pCR status is not routinely performed in clinical practice in the NHS. Therefore, for the scenario analysis where a stopping rule is applied to pembrolizumab for patients who achieve a pCR, an additional cost of £43.81 was applied for patients who receive surgery in the pembrolizumab arm based on NHS unit cost DAPS02 – "histopathology and histology".(112)

B.3.6. Severity

MSD considers that pembrolizumab does not qualify for a severity modifier in this indication as the expected QALY loss for standard of care versus the general population does not meet any severity modifier threshold.

B.3.7. Uncertainty

MSD considers that key areas of uncertainty relating to this indication have been adequately captured in the economic model and explored through sensitivity and scenario analyses.

B.3.8. Managed access proposal

As discussed in section B.2, the addition of peri-adjuvant pembrolizumab to neoadjuvant chemotherapy demonstrated a statistically significant and clinically meaningful improvement in all primary and key secondary efficacy endpoints (EFS, pCR, MPR, and OS), over 29.8 months median follow-up, compared with neoadjuvant chemotherapy alone. The economic evaluation and sensitivity analyses show that pembrolizumab treatment is a highly cost-effective strategy for managing early-stage NSCLC versus existing neoadjuvant chemotherapy and surgery alone strategies and is likely to be cost effective compared with neoadjuvant nivolumab. Given the strength of the available evidence, MSD consider that pembrolizumab should be considered for baseline commissioning as any remaining uncertainties would not be resolved by a period of managed access. However, MSD remains committed to patient access as a priority, and are willing to discuss options for managed access should it prove necessary.

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B.3.9. Summary of base-case analysis inputs and assumptions

B.3.9.1. Summary of base-case analysis inputs

The list of parameters used in the base case cost-effectiveness analysis is presented in Table 68, along with the parameters used to vary the base case inputs in sensitivity analyses, if applicable.

Table 68. 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	36.9	-	Not varied	
Discount rate: Costs	3.5%	-	Not varied	
Discount rate: Outcomes	3.5%	-	Not varied	
Starting age, years	63.1	-	Not varied	B.3.2.1
Female, %	29.4%	-	Not varied	
Body surface area, m^2	1.90	0.01	Not varied	
Weight, kg	73.7	0.6	Not varied	
Squamous histology (%)	43.2%	-	Not varied	
Non-squamous histology (%)	56.8%	-	Not varied	
Glomerular filtration rate (GFR) (mL/min/1.73 m^2)	75.0	-	Not varied	
Parameter estimates for EF→LR/P				
Parameter A, Neoadjuvant chemotherapy	4.907	-	Multivariate normal	B.3.3.1.1
Parameter B, Neoadjuvant chemotherapy	2.107	-		
Parameter C, Neoadjuvant chemotherapy	-1.097	-		
Parameter A, Pembrolizumab	5.105	-		
Parameter B, Pembrolizumab	2.768	-		
Parameter C, Pembrolizumab	-2.451	-		
Parameter estimates for EF→DM				
Parameter A, Neoadjuvant chemotherapy	4.775	-	Multivariate normal	B.3.3.1.1
Parameter B, Neoadjuvant chemotherapy	1.892	-		
Parameter C, Neoadjuvant chemotherapy	-1.543	-		
Parameter A, Pembrolizumab	5.531	-		
Parameter B, Pembrolizumab	3.009	-		
Parameter C, Pembrolizumab	-2.294	-		
Parameter estimates for EF→death				

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Parameter A, Neoadjuvant chemotherapy	7.084	-	Multivariate normal	B.3.3.1.1
Parameter B, Neoadjuvant chemotherapy	2.085	-		
Parameter A, Pembrolizumab	7.605	-		
Parameter B, Pembrolizumab	2.595	-		
Parameters for cure point				
Start of cure period, year	5	-	Not varied	B.3.3.1.1
End of cure period, year	7	-	Not varied	
Maximum risk reduction, %	95%	-	Not varied	
Parameters for time-varying HRs of EFS failure				
Pembrolizumab, d0	[redacted]	-	Multivariate normal	B.3.3.1.1
Pembrolizumab, d1	[redacted]	-		
Neoadjuvant nivolumab, d0	[redacted]	-		
Neoadjuvant nivolumab, d1	[redacted]	-		
Surgery alone, d0	[redacted]	-		
Surgery alone, d1	[redacted]	-		
Exponential rates of LR/P→DM				
Pembrolizumab	[redacted]	[redacted]	Normal	B.3.3.1.2
Neoadjuvant chemotherapy	[redacted]	[redacted]		
Neoadjuvant nivolumab	[redacted]	[redacted]		
Surgery only	[redacted]	[redacted]		
Exponential rates of LR/P→death				
Pembrolizumab	[redacted]	[redacted]	Normal	B.3.3.1.2
Neoadjuvant chemotherapy	[redacted]	[redacted]		
Neoadjuvant nivolumab	[redacted]	[redacted]		
Surgery only	[redacted]	[redacted]		
Exponential rates and HRs of OS and PFS failure by 1L DM treatment				
Pembrolizumab + pemetrexed + platinum (PDC), OS rate	0.00725	0.00043	Normal	B.3.3.1.3
Pembrolizumab + pemetrexed + platinum (PDC), PFS rate	0.01764	0.00109		
Pembrolizumab + carboplatin + paclitaxel, OS rate	0.00925	0.00076		
Pembrolizumab + carboplatin + paclitaxel, PFS rate	0.01980	0.00170		
Osimertinib, OS rate	0.00413	0.00021		
Osimertinib, PFS rate	0.00843	0.00078		
Pembrolizumab, OS rate	0.00797	0.00088		
Pembrolizumab, PFS rate	0.02452	0.00216		
Atezolizumab, OS rate	0.00789	0.00090		
Atezolizumab, PFS rate	0.01968	0.00228		
Carboplatin + paclitaxel, HR OS	1.41	0.09	Log-normal	
Carboplatin + paclitaxel, HR PFS	1.61	0.09		

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Pemetrexed + platinum (PDC), OS rate	1.67	0.09		
Pemetrexed + platinum (PDC), PFS rate	2.00	0.09		
Medical management costs				
Initial surgery costs in EF state (one-time cost), pembrolizumab	9,252.07	1,850.41	Gamma	B.3.5.2.2
Initial surgery costs in EF state (one-time cost), neoadjuvant chemotherapy	8,956.47	1,791.29		
Initial surgery costs in EF state (one-time cost), neoadjuvant nivolumab	9,383.91	1,876.78		
Initial surgery costs in EF state (one-time cost), surgery only	11,273.29	2,254.66		
Initial RT costs in EF state (one-time cost), pembrolizumab	491.15	98.23		
Initial RT costs in EF state (one-time cost), neoadjuvant chemotherapy	724.23	144.85		
Initial RT costs in EF state (one-time cost), neoadjuvant nivolumab	442.04	88.41		
Initial RT costs in EF state (one-time cost), surgery only	724.23	144.85		
Medical management costs in EF state per week, up to year 5	41.66	8.33		B.3.5.2.1
Medical management costs in EF state per week, years 5-7	21.87	4.37		
Medical management costs in EF state per week, years 7+	2.08	0.42		
Surgery cost on LR/P state entry	225.47	45.09		B.3.5.2.3
RT (as CRT) cost on LR/P state entry	1,667.11	333.42		
RT cost on LR/P state entry	1,111.41	222.28		
Drug cost (as CRT) on LR/P state entry	32.20	6.44		
Drug cost (no RT) on LR/P state entry	32.20	6.44		
Drug administration cost (as CRT) on LR/P state entry	560.77	112.15		
Drug administration cost (no RT) on LR/P state entry	560.77	112.15		
Medical management costs in LR/P state (per week)	133.25	26.65		B.3.5.2.1
Medical management costs upon DM state entry (one-time cost)	1,298.50	259.70		B.3.5.2.4

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Medical management costs in pre-progression DM state (per week)	254.04	50.81		B.3.5.2.1
Medical management costs in post-progression DM state (per week)	312.79	62.56		
Terminal care cost (one-time cost)	7,428.87	1,485.77		B.3.5.4.2
Drug administration costs				
Unit costs of IV drug administration, IO monotherapy or single agent chemotherapy	287.00	57.40	Gamma	B.3.5.1
Unit costs of IV drug administration, IO combination therapy or multiple agent chemotherapy	353.64	70.73		
Unit costs of oral drug dispensing	216.90	43.38		
AE costs				
Pembrolizumab	128.26	25.65	Gamma	B.3.3.2 and B.3.5.3
Neoadjuvant chemotherapy	117.68	23.54		
Neoadjuvant nivolumab + chemotherapy	111.00	22.20		
Surgery alone	0.00	0.00		
Utilities				
Utility of EF (without toxicity)	0.882	0.008	Beta	B.3.4.5
Utility of LR/P	0.776	0.034	Beta	
Utility of pre-progression DM	0.727	0.038	Beta	
Utility of post-progression DM - squamous	0.657	0.030	Beta	
Utility of post-progression DM - non-squamous	0.679	0.026	Beta	
Disutility from AEs	-0.091	0.016	Normal	
Disutility associated with age	-0.0002587	0.00005	Normal	
Disutility associated with age^2	-0.0000332	0.00001	Normal	
Utility associated with male gender	0.0212126	0.00424	Normal	

Abbreviations: AE, adverse event; DM, distant metastases; EF, event-free; LR/P, loco-regional recurrence or progression; PSA, probabilistic sensitivity analysis; SE, standard error.

B.3.9.2. Assumptions

A summary of the key assumptions used in the economic evaluation is provided in Table 69.

Table 69. Assumptions used in the economic evaluation

Parameter	Assumption	Justification
Cure	Patients who remain in the EF health state after 7 years are	Clinician feedback indicates that most relapsed occur in the first 5 years and

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	assumed to be functionally cured, and their risk of an event (i.e. transitioning from EF to LR/P, DM or death) is reduced by 95% relative to the risk estimated by the parametric function. A linear reduction in risk is applied gradually starting from 5 years until the 95% reduction is reached at 7 years.	that it is reasonable to assume that there will be very few, if any, recurrences or disease-related deaths after 5 years (36, 71). This is supported by the evidence from the literature (82) and is consistent with assumptions the NICE Guideline Committee made during development of NG122 (83).
Treatment effect waning	No treatment effect waning (TEW) is applied to either pembrolizumab or nivolumab so that only the selected parametric functions, cure assumption and background mortality rates determine time in the EF state.	• TEW has not typically been applied in previous NICE appraisals of pembrolizumab in early-stage settings (76, 77, 84). • With the application of the cure assumption, TEW is already effectively being applied after the cure-point as hazards are equalizing therefore additional TEW is not required. • The mechanism of action of PD-1 inhibitors supports a sustained treatment effect(86) • Observed data from KEYNOTE-671 support the plausibility of a sustained treatment effect • Long-term data from historic pembrolizumab adjuvant (and other) indications support a sustained treatment effect (87, 90-92, 125)
Comparative efficacy of nivolumab and surgery alone	Transition probabilities for neoadjuvant nivolumab and surgery alone comparators were estimated by applying time-varying HRs obtained from an NMA of clinical trials conducted in the neoadjuvant setting to the pembrolizumab arm. It was assumed that the proportion of the overall hazard attributable to each EFS failure type is the same as in the pembrolizumab arm.	Head-to-head data on the comparative efficacy of peri-adjuvant pembrolizumab versus neoadjuvant nivolumab and surgery alone were not available from the KEYNOTE-671 trial, therefore comparative estimates had to be sourced elsewhere. It was not possible to obtain separate HRs for each cause-specific hazard of transition as information on cause-specific hazards is not available for the non-pembrolizumab trials.
Transitions from the DM state	Transitions from the DM state to death were assumed to depend on the distribution of first-line treatments for metastatic NSCLC received in that arm, and the efficacy of each treatment as reported in the pivotal trials.	The distribution of first-line treatment was based on advice from UK clinicians.
Distribution of treatments for	In the first-line DM setting, 15% of patients are assumed to get a TKI.	This 15% is conservative given the proportions of patients who would be likely to present with EGFR, KRAS

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metastatic NSCLC	Efficacy and costings for this 15% are assumed to be associated with osimertinib.	G12C, ALK, or ROS-1 mutation types at DM. Osimertinib is the treatment of choice for the most common market (EGFR) and therefore it is used as a proxy for all TKIs for computational simplicity.
	Amongst patients receiving IO monotherapy, an 80:20 split of pembrolizumab to atezolizumab is assumed.	This was based on input from UK clinical experts with respect to current clinical practice (36).
	In the second-line setting, 40% of patients are assumed to receive no further active therapy (i.e. best supportive care), and that no patients will receive targeted or IO treatments at second-line as all eligible patients will have received them in the first-line setting.	
Retreatment with IO in the DM state	Patients in the pembrolizumab and nivolumab arms who enter the DM state ≥6 months after the final scheduled dose of IO are eligible for retreatment with an IO for metastatic NSCLC. In the pembrolizumab arm this is 21 months after the start of the model; in the nivolumab arm this is 8 months after the start of the model.	UK clinicians advised that NHS England would allow rechallenge with an anti-PD-(L)1 IO if recurrence occurred at least 6 months after the end of (neo)adjuvant IO treatment (6, 36). Peri-adjuvant pembrolizumab involves 17 scheduled doses Q3W whereas neoadjuvant nivolumab involves 3 scheduled doses Q3W, therefore patients treatment with nivolumab will be eligible for rechallenge sooner.
Post-recurrence efficacy	Transition probabilities from LR/P and DM health are assumed to be the same in all treatment arms, therefore it is assumed that there is no ongoing treatment effect of pembrolizumab after recurrence.	This is a conservative assumption in the absence of conclusive evidence supporting a residual treatment effect after recurrence and is explored in scenario analyses.
Adverse events	AE rates in the in the surgery alone arm were assumed to be zero.	Patients who go straight to surgery without receiving any neoadjuvant therapy do not receive active therapy and therefore are not expected to experience AEs. This is a conservative assumption, as some patients may receive subsequent adjuvant therapy which would be associated with AEs.
Pembrolizumab administration	Pembrolizumab is assumed to be administered as a 200 mg dose Q3W in the neoadjuvant setting, and as a 400 mg dose Q6W in the adjuvant setting. It is assumed that the first dose in the adjuvant setting will be 200 mg with the first 400 mg dose administered 3 weeks later.	Clinical advice indicated that clinicians would prefer to use a Q6W dosing regimen where pembrolizumab is offered less frequently at double the dose in the adjuvant phase, as it reduces the burden on NHS capacity.

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	This allows patients to be monitored as they reinitiate treatment with pembrolizumab.	
Utilities	Utility values for EF and LR/P health states, and AE disutilities, are sourced from the KEYNOTE-671 trial. Utility values for the post-progression DM health state are sourced from trials of pembrolizumab in the first-line metastatic setting (KEYNOTE-189 and KEYNOTE-407).	EQ-5D data corresponding to post-progression DM were not available from KEYNOTE-671 as the available follow-up from the trial was too limited to enable a robust analysis of post-progression utility.
	The EF utility value did not include Grade 1-2 AEs, and therefore reflected patients in the EF health state without any adverse events. The HRQoL impact of Grade 3+ AEs was captured by applying a disutility to the proportion of patients experiencing a Grade 3+ AE KEYNOTE-671.	This approach best reflects the utility of the EF health state over the whole model time horizon. Cured patients may survive for decades in the EF state but most EQ-5D forms were completed during the first year of the trial, therefore including Grade 1-2 AEs would underestimate the utility of the health state.
Vial sharing	Vial sharing is assumed to be not permitted for any treatments.	In line with the NICE reference case.

Abbreviations: AE, adverse event; DM, distant metastases; EF, event-free; EFS, event-free survival; IO, immunotherapy; LR/P, loco-regional recurrence or progression; NHS, National Health Service; NMA, network meta-analysis; NSCLC, non-small-cell lung cancer; Q3W, every 3 weeks; TEW, treatment effect waning; TKI, tyrosine kinase inhibitor.

B.3.10. Base-case results

B.3.10.1. Base-case incremental cost-effectiveness analysis results

The deterministic base case cost-effectiveness results are presented in Table 70. The model estimated that peri-adjuvant pembrolizumab resulted in 2.14 discounted additional life years compared with neoadjuvant chemotherapy, and 3.04 discounted additional life years versus the surgery alone approach. This translated into an additional [redacted] and [redacted] QALYs, respectively. The incremental cost-effectiveness ratio (ICER) was [redacted] versus neoadjuvant chemotherapy and [redacted] versus surgery alone, indicating that peri-adjuvant pembrolizumab is a highly cost-effective strategy when considering these standard treatment options. Compared with neoadjuvant nivolumab, the model estimated that peri-adjuvant pembrolizumab generated in 1.03 additional life years and [redacted] additional QALYs, which resulted in an ICER of [redacted].

The disaggregated base case results are shown in Appendix J.

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Table 70. Base-case deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus comparator (£/QALY)
Peri-adjuvant pembrolizumab	[redacted]	8.31	[redacted]	-	-	-	-
Neoadjuvant chemotherapy	[redacted]	6.17	[redacted]	[redacted]	2.14	1.91	[redacted]
Neoadjuvant nivolumab + chemotherapy	[redacted]	7.28	[redacted]	[redacted]	1.03	0.90	[redacted]
Surgery alone	[redacted]	5.28	[redacted]	[redacted]	3.04	2.64	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.
Incremental results are for pembrolizumab + chemotherapy versus the comparator technology.

Table 71. Fully incremental base case deterministic results

Fully incremental results	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus reference (£/QALY)
Neoadjuvant nivolumab + chemotherapy	[redacted]	7.28	[redacted]	Reference	Reference	Reference	Reference
Surgery alone	[redacted]	5.28	[redacted]	[redacted]	-2.00	-1.742	[redacted]
Neoadjuvant chemotherapy	[redacted]	6.17	[redacted]	[redacted]	-1.11	-1.017	[redacted]
Peri-adjuvant pembrolizumab	[redacted]	8.31	[redacted]	[redacted]	1.03	0.896	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.
Fully incremental costs and QALYs are calculated using the least costly treatment arm as the reference arm. Fully incremental ICERs are calculated versus the next less expensive treatment that is not dominated or extendedly dominated.

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B.3.10.2. Exploring uncertainty

To explore the uncertainty around the parameters and assumptions used in the economic model, a series of sensitivity and scenario analyses were conducted.

B.3.10.3. Probabilistic sensitivity analysis

To explore the uncertainty around the variables included in the economic model, probabilistic sensitivity analysis (PSA) was performed by running the analysis over 1,000 simulations. The distributions used to vary model parameters are presented in section B.3.9.1 (Table 68).

The cost-effectiveness results obtained from the PSA are shown in Table 72; the corresponding scatterplots of PSA results and cost-effectiveness acceptability curves (CEAC) are shown in Figure 22 and Figure 23, respectively. The probabilistic results are very similar to those in the deterministic base case. The PSA results demonstrate that, under base case assumptions, there is a [redacted]% probability that peri-adjuvant treatment with pembrolizumab is a cost-effective treatment strategy versus chemotherapy or surgery alone and a [redacted]% probability that it is cost-effective versus nivolumab at a threshold of £30,000/QALY gained. There was an 85% probability that peri-adjuvant pembrolizumab generated more QALYs than neoadjuvant nivolumab.

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Table 72. Probabilistic cost-effectiveness results (mean of 1,000 iterations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab + chemotherapy vs:							
Pembrolizumab + chemotherapy	[redacted]	**8.20**	[redacted]	-	-	-	-
Neoadjuvant chemotherapy	[redacted]	6.17	[redacted]	[redacted]	2.03	1.82	[redacted]
Neoadjuvant nivolumab + chemotherapy	[redacted]	7.21	[redacted]	[redacted]	0.99	0.86	[redacted]
Surgery alone	[redacted]	5.16	[redacted]	[redacted]	4.17	3.04	[redacted]

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

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Figure 22: PSA scatterplot - pembrolizumab versus nivolumab

A) Pembrolizumab vs neoadjuvant chemotherapy

B) Pembrolizumab vs neoadjuvant nivolumab

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C) Pembrolizumab vs surgery alone

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 23. Cost-effectiveness acceptability curve

Abbreviations: QALY, quality-adjusted life year.

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B.3.10.4. Deterministic sensitivity analysis

One-way deterministic sensitivity analyses (DSA) were conducted to explore the uncertainty in the cost-effectiveness results and identify key model drivers. Parameters were varied by their 95% confidence intervals, or by ±20% if measures of variance were not available. The following variables were explored in the DSA:

- Exponential rates of transitions from LR/P health state
- Exponential rates of OS and PFS failure with first-line treatments for metastatic NSCLC
- Unit costs of drug administration
- Patient weight, body surface area and GFR
- Initial surgery and adjuvant radiotherapy costs in the EF state
- Medical management costs in the EF state
- Chemotherapy, salvage surgery and radiotherapy costs on LR state entry
- Medical management costs in the LR state
- Medical management costs in the DM state (upon entry, pre-progression and post-progression)
- Terminal care costs
- Adverse event costs
- Health state utilities and disutilities from adverse events

The results of the DSA are presented in a tornado diagram (Figure 24) which illustrates the 10 parameters that had the most impact on the ICER. No individual parameters had a large effect on the ICER of pembrolizumab versus nivolumab.

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Figure 24. Tornado diagram featuring top 10 individually influential parameters

A) Pembrolizumab vs neoadjuvant chemotherapy

B) Pembrolizumab vs neoadjuvant nivolumab

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C) Pembrolizumab vs surgery alone

Abbreviations: CI, confidence interval; DM, distant metastases; EF, event-free; ICER, incremental cost-effectiveness ratio; IV, intravenous; LR, loco-regional recurrence or progression; QALY, quality-adjusted life year.
* Indicates sensitivity analyses in which peri-adjuvant pembrolizumab is dominant over the comparator.

B.3.10.5. Scenario analysis

A series of scenario analyses was conducted to explore the uncertainty around key structural and methodological assumptions, and sources of data used to inform model inputs. The results of all scenarios are presented in Table 73. These demonstrate that peri-adjuvant treatment with pembrolizumab remains a cost-effective strategy across a wide range of alternative plausible modelling assumptions.

One set of scenario analyses explores “Whether pembrolizumab is used before and after surgery,” which was identified as a subgroup in the NICE scope. As discussed in section B.1.3.2, clinical feedback indicated that clinicians may wish to stop treatment with pembrolizumab for patients who achieve a pCR. As KEYNOTE-671 was not designed to formally assess outcomes based on using pCR as a stopping criteria, a formal subgroup analysis was not possible. Instead, a series of exploratory scenario analyses is considered with the simplifying assumption that the clinical outcomes with pembrolizumab under this treatment strategy would be identical to those in the ITT population. It was assumed that patients who achieve a pCR (18.1%) did not incur any further pembrolizumab treatment costs. The additional cost of testing for pCR status was added to the surgery costs in this scenario (see section B.3.10.5). The analysis was set up this way as EFS curves appear very similar among pCR patients in KEYNOTE-671 and Checkmate 816 (Figure 27 and

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Figure 28). This suggests the contribution of adjuvant pembrolizumab among the pCR population may have been a negligible proportion of the overall treatment effect observed in KEYNOTE-671 (i.e. the treatment effect is principally or entirely caused by increasing pCR rates and improving outcomes among those who didn't achieve a pCR).

[redacted]. This may be an indicator of the benefit of adjuvant treatment among patients not achieving a pCR.

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Figure 25 EFS outcomes for pembrolizumab by pCR status

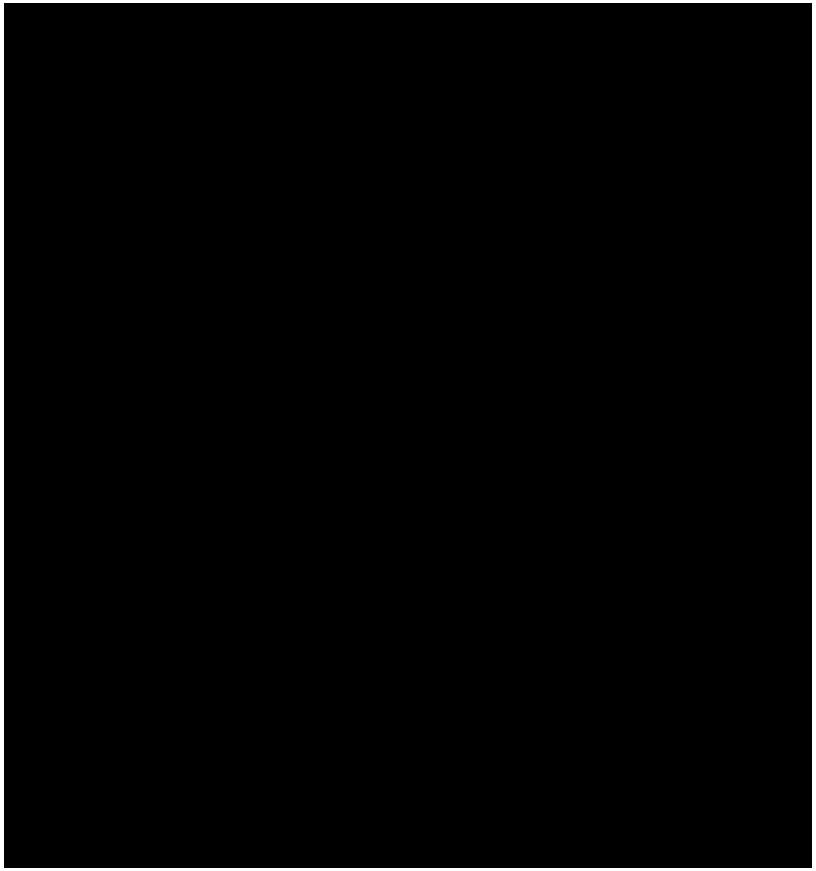

Figure 26. EFS outcomes for nivolumab by pCR status

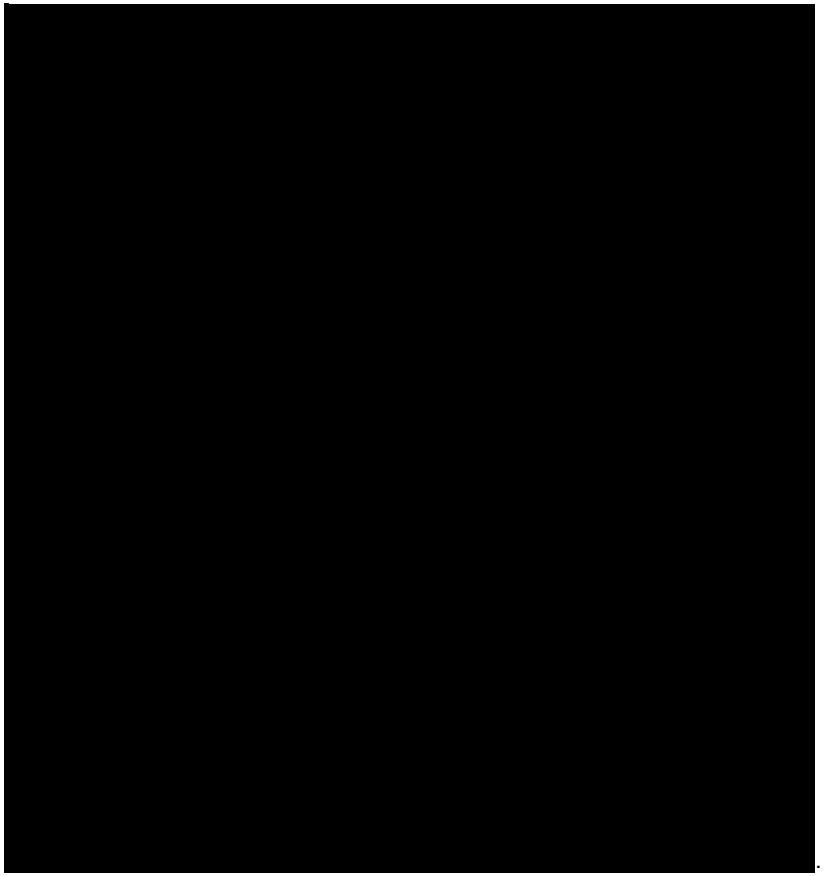

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Table 73. Scenario analyses

#	Scenario	Description	Vs chemotherapy			Vs nivolumab			Vs surgery		
			Δ Costs (£)	Δ QALY	ICER (£/QALY)	Δ Costs (£)	Δ QALY	ICER (£/QALY)	Δ Costs (£)	Δ QALY	ICER (£/QALY)
-	**Base case**	-	[redacted]	**1.91**	[redacted]	[redacted]	**0.90**	[redacted]	[redacted]	**2.64**	[redacted]
1	Alternative functions for modelling of transitions from EF state (Approach #1; EF→LR/P, EF→DM, EF→death)	Alternative EF→death distribution Gen gamma/ Gen gamma/ Gen gamma	[redacted]	2.10	[redacted]	[redacted]	0.84	[redacted]	[redacted]	2.66	[redacted]
2		2nd best-fitting in chemo arm Gompertz/ Gen gamma/ Log-normal	[redacted]	1.87	[redacted]	[redacted]	0.86	[redacted]	[redacted]	2.64	[redacted]
3		2nd best-fitting in pembro arm Gen gamma/ Gompertz/ Log-normal	[redacted]	2.02	[redacted]	[redacted]	0.83	[redacted]	[redacted]	2.66	[redacted]
4	Alternative approaches for modelling transitions from EF state	Approach #2 (time-constant HR): Gompertz/ Gompertz/ Gompertz	[redacted]	1.71	[redacted]	[redacted]	0.88	[redacted]	[redacted]	2.62	[redacted]
5		Approach #3 (time-varying HR): Gompertz/ Gompertz/ Gompertz	[redacted]	1.93	[redacted]	[redacted]	0.84	[redacted]	[redacted]	2.64	[redacted]
6	Alternative cure assumptions	Cure period 3-5 years (95% of patients cured at 5 years)	[redacted]	1.87	[redacted]	[redacted]	0.72	[redacted]	[redacted]	2.65	[redacted]
7		Cure period 5-10 years (95% of patients cured at 10 years)	[redacted]	1.93	[redacted]	[redacted]	0.95	[redacted]	[redacted]	2.63	[redacted]
8		Cure period 7-10 years (95% of patients cured at 10 years)	[redacted]	1.92	[redacted]	[redacted]	0.99	[redacted]	[redacted]	2.62	[redacted]
9		100% patients cured at end of 5-7 year cure period	[redacted]	1.91	[redacted]	[redacted]	0.89	[redacted]	[redacted]	2.64	[redacted]
10	Time-varying HR NMA for external comparators:	Time-varying HR vs pembrolizumab not held constant after end of trial	[redacted]	1.91	[redacted]	[redacted]	0.90	[redacted]	[redacted]	2.64	[redacted]
11		Time-varying HR vs pembrolizumab trends to 1 at 5-7 years	[redacted]	1.91	[redacted]	[redacted]	0.86	[redacted]	[redacted]	2.60	[redacted]

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12	Alternative assumptions	Time-varying HR vs pembrolizumab not held constant after end of trial + Cure period 7-10 years	[redacted]	1.92	[redacted]	[redacted]	1.00	[redacted]	[redacted]	2.62	[redacted]
13		Time-varying HR vs pembrolizumab trends to 1 at 5-7 years + Cure period 7-10 years	[redacted]	1.92	[redacted]	[redacted]	0.83	[redacted]	[redacted]	2.49	[redacted]
14		Weibull random-effects time-varying HR NMA	[redacted]	1.91	[redacted]	[redacted]	0.91	[redacted]	[redacted]	2.68	[redacted]
15		Gompertz fixed-effects time-varying HR NMA	[redacted]	1.91	[redacted]	[redacted]	0.67	[redacted]	[redacted]	2.62	[redacted]
16		Gompertz random-effects time-varying HR NMA	[redacted]	1.91	[redacted]	[redacted]	0.68	[redacted]	[redacted]	2.67	[redacted]
17	Time-constant HR NMA for external comparators	Time-constant EFS HRs for nivolumab and surgery vs pembrolizumab	[redacted]	1.91	[redacted]	[redacted]	0.49	[redacted]	[redacted]	2.41	[redacted]
18		Time-constant EFS HRs for nivolumab and surgery vs pembrolizumab + Cure period 3-5 years	[redacted]	1.87	[redacted]	[redacted]	0.47	[redacted]	[redacted]	2.41	[redacted]
19		Time-constant EFS HRs for nivolumab and surgery vs pembrolizumab + Cure period 7-10 years	[redacted]	1.92	[redacted]	[redacted]	0.50	[redacted]	[redacted]	2.40	[redacted]
20	Adjustment factor for transitions from DM	No adjustment of DM→death transitions based on SEER Medicare	[redacted]	1.89	[redacted]	[redacted]	0.89	[redacted]	[redacted]	2.62	[redacted]
21	Calibration of downstream transitions to observed OS	LR/P→death transitions temporarily calibrated over maximum trial follow-up (i.e. 5 years) to achieve better fit to observed OS	[redacted]	2.08	[redacted]	[redacted]	0.92	[redacted]	[redacted]	2.78	[redacted]
22		LR/P→DM and LR/P→death transitions temporarily calibrated over maximum trial follow-up (i.e. 5	[redacted]	2.11	[redacted]	[redacted]	0.91	[redacted]	[redacted]	2.81	[redacted]

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		years) to achieve better fit to observed OS									
23		Transitions from LR/P and DM states temporarily calibrated over maximum trial follow-up (i.e. 5 years) to achieve better fit to observed OS	[redacted]	2.07	[redacted]	[redacted]	0.91	[redacted]	[redacted]	2.78	[redacted]
24	pCR stopping rule	Patients who are identified at surgery as having achieved pCR are assumed not to receive adjuvant pembrolizumab	[redacted]	1.91	[redacted]	[redacted]	0.90	[redacted]	[redacted]	2.64	[redacted]
25		pCR stopping rule + Gompertz fixed-effects time-varying HR NMA	[redacted]	1.91	[redacted]	[redacted]	0.67	[redacted]	[redacted]	2.62	[redacted]
26		pCR stopping rule + Time-constant HR NMA	[redacted]	1.91	[redacted]	[redacted]	0.49	[redacted]	[redacted]	2.41	[redacted]
27	Alternative market shares of systemic therapy in the DM state	20% of patients assumed not to receive active 1L treatment for NSCLC (see Appendix M.3.2)	[redacted]	1.98	[redacted]	[redacted]	0.92	[redacted]	[redacted]	2.69	[redacted]
28	Alternative sources of utility values	EF utility from KEYNOTE-671 includes Grade 1-2 AEs (0.830)	[redacted]	1.76	[redacted]	[redacted]	0.83	[redacted]	[redacted]	2.45	[redacted]
29		Post-progression DM utility from KEYNOTE-671 (0.727)	[redacted]	1.89	[redacted]	[redacted]	0.89	[redacted]	[redacted]	2.62	[redacted]
30	Alternative dosing schedule for pembrolizumab	Pembrolizumab dosing schedule 200 mg Q3W in adjuvant setting	[redacted]	1.91	[redacted]	[redacted]	0.90	[redacted]	[redacted]	2.64	[redacted]
31	Pessimistic composite scenario 1	• Gompertz fixed-effects time-varying HR NMA • Time-varying HR vs pembrolizumab trends to 1 at 5-7 years • Cure period 7-10 years	[redacted]	1.84	[redacted]	[redacted]	0.59	[redacted]	[redacted]	2.34	[redacted]

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		• 20% patients do not receive 1L DM treatment • EF utility includes Grade 1-2 AEs • Q3W dosing in adjuvant setting									
32	Pessimistic composite scenario 2	• 31 + pCR stopping rule	[redacted]	1.84	[redacted]	[redacted]	0.59	[redacted]	[redacted]	2.34	[redacted]

Abbreviations: AE, adverse event; DM, distant metastases; EF, event-free; EFS, event-free survival; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LR/P, locoregional recurrence or progression; NMA, network meta-analysis; NSCLC, non-small-cell lung cancer; OS, overall survival; pCR, pathological complete response; QALY, quality-adjusted life year; QxW, every x weeks.

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B.3.11. Subgroup analysis

Subgroup analysis was not performed as it is not considered relevant for this indication.

B.3.12. Benefits not captured in the QALY calculation

MSD consider that the benefit of pembrolizumab has been adequately captured in the economic evaluation.

B.3.13. Validation

B.3.13.1. Validation of cost-effectiveness analysis

To verify the results of the cost-effectiveness model, quality control procedures were undertaken to ensure that the mathematical calculations are performed correctly and are consistent with the model's specifications, and that parameter input values are correctly populated throughout the model.

The internal validity of the model was also assessed by comparing modelled efficacy outcomes against the original sources that informed the efficacy inputs. The present economic model was developed using efficacy data from the recent efficacy report from KEYNOTE-671 (data cutoff date: 10-July-2023), representing 36.6 months of median follow-up. Specifically, the EFS curves predicted for the two arms of KEYNOTE-671 were plotted alongside the observed Kaplan-Meier curves for EFS to ensure that the curves are well-aligned during the trial period. Similar comparisons were conducted between the predicted and observed cumulative incidence curves for each individual transition from the event-free state (i.e., EF→LR/P, EF→DM, and EF→death).

Model predictions were also compared against observed data from an external study. Specifically, data from the SEER-Medicare KN671-matched cohort were used to validate the model predictions for EFS and OS in the placebo arm. Details are provided in section B.3.3.1.1.

Additionally, a total of 12 clinical experts treating NSCLC within the UK NHS were consulted across two advisory boards to validate and inform the key model assumptions, such as cure, subsequent treatments and resource use post-recurrence or progression from a clinical perspective.

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B.3.14. Interpretation and conclusions of economic evidence

To date, NICE have conducted three Technology Appraisals in the early NSCLC setting and all used slightly different model structures. The current model was most similar to the only other model used in the neo-adjuvant setting, having four health states to represent the distinct stages of the patient pathway; Event-Free, Loco-regional recurrence/Progression, Distant Metastases and Death. While this structure simplifies the pathway, it has the advantage of transparency, model parsimony, minimising the use of assumptions and uncertain evidence and has been used in many previous NICE Technology Appraisals of interventions for early-stage cancers. The model made use of the best available evidence and extensive scenario analyses. The primary treatment effects were drawn from the pivotal RCT and network meta-analyses of parallel RCTs that were directly relevant to the decision problem, whilst intermediate health states were drawn from real world evidence or from large, high quality RCTs. Utility estimates were sourced directly from the trial and resource estimates were obtained from two advisory boards along with inputs agreed during two previous appraisals.

Pembrolizumab is modelled to affect QALYs by delaying recurrence and by increasing the proportion of patients who are genuinely cured by their radical treatment plan. The increased costs of peri-adjuvant treatment are offset to a large degree by savings from managing and treating recurrent and metastatic NSCLC.

Incremental cost-effectiveness ratios for pembrolizumab versus the two long-standing standard treatment options, surgery alone and chemotherapy + surgery, were very low in all scenarios tested. The model provides very strong evidence that pembrolizumab is cost-effective versus these strategies, including in 100% of iterations in the PSA. There is more uncertainty about whether pembrolizumab is cost-effective versus the neoadjuvant nivolumab regimen. The base case ICER was below NICE's typical threshold of £20,000-£30,000/QALY gained but some scenarios were above this threshold. However, the clinical evidence in favour of pembrolizumab appears stronger and more generalisable than that from CheckMate-816, which was a smaller open-label trial conducted in less generalisable geographies with inconsistency of effects across its subgroups and with a HR that visually appears to be consistently trending upwards over time, particularly among patients who did not achieve a pCR. In contrast, KEYNOTE-671 enrolled more than double the number of patients, was conducted double-blind, had consistent effects across subgroups and a HR that was consistently trending downwards over time, being statistically significant at all time points across the time horizon. There was an [redacted] probability that peri-adjuvant

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pembrolizumab generated more QALYs than neo-adjuvant nivolumab and a [redacted] probability that it was more cost-effective.

Several scenarios did not meaningfully affect the ICERs; the model appears insensitive to the choice of EFS survival curve extrapolation and to assuming cure occurs at later time points. The model's conclusions were also qualitatively unaffected by calibration to correct for underprediction of OS benefit for peri-adjuvant pembrolizumab but this is largely because we chose the conservative assumption of imposing the same calibration on the neoadjuvant nivolumab arm.

The most influential scenario analysis was whether relative treatment effects were calculated using a time-varying or time-constant NMA. The time-varying model was used in the base case due to a consistent trend in reduction in HR being observed in one key study and a consistent trend in increase in HR being observed in the other. This trend was frozen between the end of observed follow-up and the cure point as a conservative measure. As parametric curves are routinely fitted independently to trial arms in NICE Technology Appraisals of oncology interventions, it is implicitly routine to use time-varying treatment effects for direct comparators. Because of this, the company believes it is logical to also consider time-varying treatment effects for indirect comparators, particularly when there is biological plausibility for a reduction of effect given the differences in number of treatment cycles and timing of surgery between regimens.

Other key scenarios of interest considered whether pembrolizumab would be used in (the 18.1% of) patients who achieved a pCR after neoadjuvant therapy or not. Given the very low recurrence rates among pCR patients observed in CheckMate-816 (where there was no adjuvant immunotherapy), it is unclear whether the results of KEYNOTE-671 would have been any different if pCR patients had not received adjuvant treatment. Most clinicians at the UK advisory board expressed the view that they would not continue adjuvant treatment if a patient received a pCR. The ICERs were much lower in scenarios that removed adjuvant treatment costs from pCR patients.

The company conducted a pessimistic scenario analysis which made several conservative choices in combination and the ICER versus neoadjuvant nivolumab remained below £30,000/QALY gained.

Taken together, the cost-effectiveness evidence shows that peri-adjuvant treatment with pembrolizumab is certain to be cost-effective versus traditional treatment options and likely to be cost-effective versus neoadjuvant nivolumab.

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B.4. References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID5094]

Summary of Information for Patients (SIP)

March 2024

File name	Version	Contains confidential information	Date
NICE ID5094_Pemrolizumab neoadjuvant and adjuvant NSCLC_SIP	1.0	No	26 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

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 is being appraised in combination with platinum-containing chemotherapy as neoadjuvant treatment, then continued as monotherapy for adjuvant treatment, of resectable non-small cell lung cancer (NSCLC) at high risk of recurrence in adults. A neoadjuvant treatment is used before surgery, and an adjuvant treatment is used after surgery. The goal of adding treatments to surgery is to reduce the risk of the cancer coming back. Even if all the tumour is removed during surgery, there might be some cancerous cells left behind, which might move through the body to other sites. The body has something called an immune response, which is a reaction to protect the body against anything unusual that enters the body. Drugs called immunotherapies act by triggering the immune response and helping the immune system to fight, amongst other things, cancer. Pembrolizumab is an immunotherapy. Giving pembrolizumab before and after surgery (also known as peri-adjuvant or peri-operative) helps the body to target and kill any cells that are there before the surgery and that might be released during the surgery. The types of patient who will be able to have pembrolizumab are described in section 1c.

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.

UK marketing authorisation for pembrolizumab is pending. Further details are available in the main submission (section B.1.2, table 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	
Helen Rollason Cancer Charity	N	N	
Independent Cancer Patients Voice	N	N	
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	
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

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.[1] These cells grow to form tumours. 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.[1] NSCLC is also the most frequent (approximately 88% of lung cancer cases).[2] The indication being looked at by NICE only involves NSCLC. The spread of a cancer is classified by stage, where stage I refers to early stage cancer and stage IV to more advanced stages.[3] Stage I means that the cancer has been caught early and has not spread to other sites in the body, possibly far away from the lung, which is termed metastases or metastatic disease. Stage I cancers have much better outcomes than stage IV cancers. Tumours at stages II-III are somewhere in between and are larger size than those at stage I and might have spread to the lymph nodes or to other areas near the lung, but not to distant sites, which is stage IV. Lung cancer is the second most common cancer type and the main cause of cancer death worldwide.[1] In the UK, it is the third most common cancer;[4] around 35,000 people were diagnosed with lung cancer in England in 2021.[2] Lung cancer is the most common cause of cancer death in the UK (34,771 on average every year, which is 21 out of 100 of all cancer deaths).[5] Overall, only 45 out of 100 people diagnosed with lung cancer in England are alive one year or more after diagnosis. The percentage of people surviving their cancer when their cancer is caught at early stage is much higher, and can be as high as 88 out of 100 people, depending on the stage of cancer at diagnosis.[6] Lung cancer can be hard to diagnose as in the early stages a patient might not have any symptoms and could feel well, which is called asymptomatic disease.[7] It is often only in the later stages of disease that a person might start having symptoms, such as coughing a lot, coughing up blood (haemoptysis), being out of breath, feeling tired, and chest pain.[7, 8] Sometimes, lung cancer is caught early because a person might have a chest examination for another reason.[7, 8]

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 have different tests to get a picture of the lungs, to confirm the diagnosis and determine the stage of the disease.[8] Tests include X rays of the chest, and contrast-enhanced chest CT. Sometimes it might be necessary to take a sample from the lung (a biopsy) to check for certain mutations in genes or other markers that will help in choosing the best treatment for a patient. For pembrolizumab, and other immunotherapies, tests can be carried out to see how many cells express (produce) a biomarker called programmed death-ligand 1 (PD-L1). But the test is not required when pembrolizumab is used before and after surgery.

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.

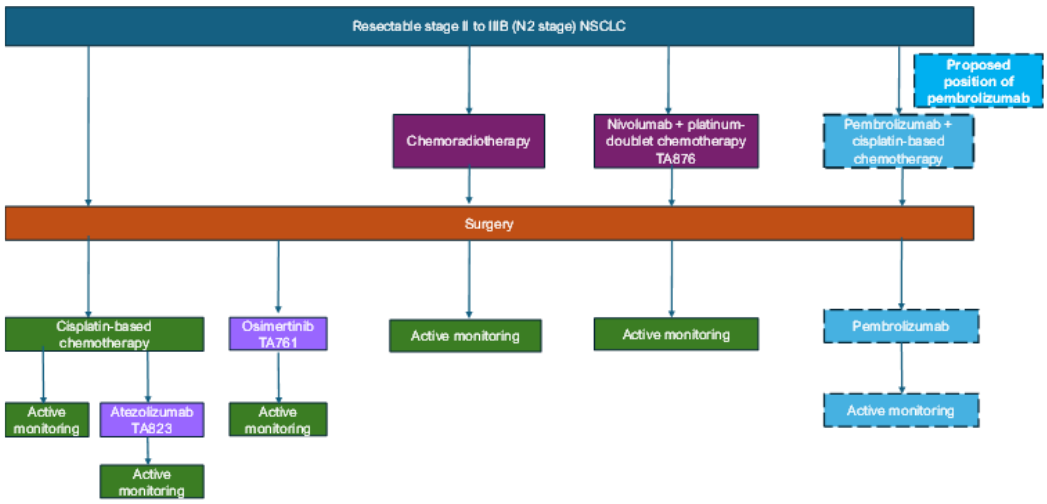
In early-stage NSCLC (stages I-IIIA), the main treatments of choice are delivered with the purpose of eliminating the cancer and making sure the patient remains cancer free for as long as possible.[9] If the tumour can be removed, surgery is the favoured treatment.[9] Some people will not be well enough to have surgery, it might be that their lungs and heart are not working properly. Some people will choose not to have surgery. Patients who do not want to have surgery or who cannot have surgery can receive radiotherapy.[9]

Chemotherapy after surgery (adjuvant treatment) is an option to further reduce the risk of recurrence.[9] 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. Patients' suitability to the adjuvant treatment depends on many factors, including other conditions they may have and recovery after surgery.

There are several options available to patients with NSCLC that is resectable (shown in the figure below), the choice of which is influenced by whether the medical team think it best for the patient to go straight to surgery. One option available is to have an immunotherapy called nivolumab plus chemotherapy before surgery.[10] If it is thought best to go straight to surgery, two drugs available to patients are : atezolizumab for patients whose tumours have the PD-L1 biomarker expression on 50% or more of their tumour cells,[11] and osimertinib for patients whose tumours carry a specific mutation (EGFR).[12] Atezolizumab and osimertinib are currently recommended within the Cancer Drugs Fund, which is a time-limited source of funding and gives the companies more time to gather more data on how well their drugs work. For patients who cannot have any of the options available, surgery and adjuvant chemotherapy (where suitable) are the preferred treatment.[9]

Through this appraisal MSD are aiming to seek a NICE recommendation for pembrolizumab for resectable non-small cell lung cancer (NSCLC) at high risk of recurrence. These are patients with high unmet medical need as there is no treatment option available where patients can receive immunotherapy both before and after surgery. The diagram below shows the proposed positioning of pembrolizumab (blue boxes with dashed outline), subject to this appraisal.

Figure 1: Proposed position of pembrolizumab for early stage NSCLC



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 face 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.[1] A review of available evidence on symptoms after surgery found that scores associated with the severity of the symptoms remained much worse at 3–4 months after surgery compared with scores before surgery.[13] Dyspnoea can have a tremendous impact on everyday life, and the study found that people were still experiencing shortness of breath even 2–3-years after surgery. Some patients reported spending most of the day in bed in the previous 12 months because of respiratory symptoms. In another study, survivors described themselves as so breathless they could not leave the house.[14]

Some patients receive chemotherapy after surgery. Chemotherapy often has side effects, which can affect people's day-to-day living.[15] People have different side effects from chemotherapy, and different chemotherapy drugs cause different side effects. Many people feel fine for the first few hours after chemotherapy.[16] Usually, some reaction occurs about four to six hours later.[16] But, some people do not react until 12 or even 24 to 48 hours after treatment. Some of the most common side effects are:[16]

- 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 can last for a long time after stopping treatment for cancer.[17] 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.[18] This can also result in significant psychological distress and reduced quality of life (QOL).[18]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

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

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, 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.

Pembrolizumab will be used with other medications (see section 3c for details).

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?

The treatment, given in a hospital through an infusion into the vein, consists of two phases.
The first is neoadjuvant therapy, given before a patient undergoes surgery. This regimen is pembrolizumab in combination with two chemotherapy drugs. One is cisplatin and the other is either gemcitabine or pemetrexed, depending on the type of lung cancer a patient has. The drugs are given across a cycle which is 21 days long. Details on the dose and length of treatment is given below.

Table 1: Summary of drugs used in KEYNOTE-671

Drug	Dose	Given	Length
Pembrolizumab	200 mg	On day 1, every 3 weeks	For 4 cycles
Cisplatin	75 mg per metre squared of body surface (m^2)	On day 1, every 3 weeks	For 4 cycles
Gemcitabine	100 mg per m^2 of body surface	On day 1 and 8 of 21 day cycle	For 4 cycles
Pemetrexed	500 mg per m^2 of body surface	On day 1, every 3 weeks	For 4 cycles

After surgery pembrolizumab is giving as an adjuvant treatment. This is given on day 1 of a 21 day cycle for up to 13 cycles.

In line with its marketing authorisation pembrolizumab may also be given at a dose of 400 mg every 6 weeks.

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.

The following clinical trials are relevant for pembrolizumab in early stage lung cancer.

Table 2: Relevant current pembrolizumab clinical trials

Study Title	NCT Number	Status	Phase

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
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
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
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
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
Study of Pembrolizumab/Vibostolimab (MK-7684A) in Combination With Concurrent Chemoradiotherapy Followed by Pembrolizumab/Vibostolimab Versus Concurrent Chemoradiotherapy Followed by Durvalumab in Participants With Stage III Non-small Cell Lung Cancer (MK-7684A-006/KEYVIBE-006)	NCT05298423	Recruiting	3

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-671 study was conducted to see how well pembrolizumab and chemotherapy worked in patients with early-stage NSCLC before and after they underwent surgery to remove the tumours, in comparison with placebo (medically inert treatment) and chemotherapy.

To find this out the following key measures were taken:

Event free survival – Event-free survival, or EFS, measures how long a person lives (from the start of the trial) without one of the following: disease or local progression, inability to resect tumour, local or distant recurrence, or death.

Taking the median, an average, typically measured in months or weeks, EFS in a trial can be a useful measure of how long a patient may expect to live without one of the events listed above.

The hazard ratio (HR) measures the average risk of experiencing an event 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 in a trial 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.

EFS results – KEYNOTE-671 demonstrated an increased benefit for the patients treated with pembrolizumab and chemotherapy compared with placebo and chemotherapy. The hazard ratio for EFS was 0.59 (95% CI: 0.48, 0.72), which corresponds to 41% reduction in the risk of the cancer coming back, progressing 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. The 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 29 months more without an event compared to patients in the placebo group (median EFS of 47.2 months versus 18.3 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 and chemotherapy compared to patients in the placebo and chemotherapy group, with HR of 0.72 (95% CI: 0.56, 0.93). The median in the pembrolizumab group is NR which refers to “Not Reached”. For the placebo group the median survival time is 52.4 months. However, a low number of deaths had occurred before the analysis of survival was carried out, which means that it is too early to say with confidence the actual benefit of pembrolizumab in reducing the risk of dying. More data on survival needs to be collected before a conclusion on the effect of pembrolizumab on survival can be made.

More information is provided in the submission document B, section B.2.6.2.

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-671 study by using two types of questionnaire, the EORTC QLQ-C30, that looks specifically at the quality of life of cancer patients, and the EQ-5D, that looks at the general health status of a patient.

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-671 study these outcomes were collected before the study patients received the treatment (baseline), at week 11 during the neoadjuvant phase and at week 10 of the adjuvant phase. These dates were chosen as it is where a high proportion of patients were 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 the EORTC and EQ-5D VAS methods, the scores decreased relative to baseline showing deterioration in the pembrolizumab arm and placebo arm in the neoadjuvant phase, and in the adjuvant phase, scores were stable relative to baseline in both the pembrolizumab arm and placebo arm.

More information is provided in the submission document B, section B.2.6.1 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-671 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 at least one adverse event was similar in the pembrolizumab group compared with the placebo group (99.5% vs 98.7%). The adverse events that were reported in at least 20% of patients in one or both treatment groups were nausea, neutrophil count decrease, anaemia, constipation, fatigue, decreased appetite, white blood cell count decreased and vomiting.

Table 3: KEYNOTE-671 Most frequent adverse events (occurred in 20% or more of patients in either arm)

Adverse event	**Pembrolizumab + chemotherapy N**	**(%)**	**Placebo + chemotherapy N**	**(%)**
Participants in population	396		399	
with one or more adverse events	394	99.5	394	98.7

Nausea	229	57.8	213	53.4
Neutrophil count decreased	174	43.9	170	42.6
Anaemia	169	42.7	166	41.6
Constipation	155	39.1	146	36.6
Fatigue	125	31.6	101	25.3
Decreased appetite	115	29.0	102	25.6
White blood cell count decreased	112	28.3	102	25.6
Vomiting	83	21.0	69	17.3

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.
- Most of the side effects that patients can experience while on treatment or after treatment are of mild or moderate severity. Overall, the benefit-risk ratio for pembrolizumab in this indication is considered positive.
- While 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 and there is the potential for pembrolizumab to be given every 6 weeks in the adjuvant setting, which could result in short 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' cancer will respond to treatment and it may not 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-671 to predict clinical effectiveness (efficacy) and costs over 36.9 years. The model comprises of four-health states: disease free, local-regional recurrence, distant metastases, and death. One challenge of modelling average lifetime outcomes (overall survival, efficacy of downstream treatments and quality-of-life) from trial data is that 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) were estimated from alternative sources.

In early-stage appraisals, the efficacy and costs of downstream treatments or subsequent treatments are an important consideration, and were therefore captured in the KEYNOTE-671 model. The efficacy of metastatic treatments was modelled based on data from published trials in the metastatic setting.

No clinical trial data were available comparing the efficacy of pembrolizumab given before and after surgery to either surgery alone or nivolumab given before surgery. To address this the these treatment strategies were compared indirectly using a methodology called network meta analysis. As these comparisons are uncertain an extensive range of alternative analyses were conducted to explore this uncertainty.

Quality-of-life data (disease free and local-regional recurrence health states and adverse events) were available from the KEYNOTE-671 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).

Differences in costs in the model are driven by the cost of pembrolizumab, which is offset by lower subsequent treatment and disease management costs in the distant metastases health state compared with surgery alone, chemotherapy or neoadjuvant nivolumab. 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.

The base-case results cannot be shared due to confidentiality. For the comparisons with chemotherapy and surgery, pembrolizumab was below the threshold of £20,000 per QALY in all scenarios explored. For the comparison with nivolumab plus chemotherapy the ICER was below £20,000 per QALY in the base case but above £30,000 for some scenarios because the model results are sensitive to the choice of methodology used to conduct the comparisons of effectiveness across different clinical trials. The ICERs described here may be different to the decision making ICERs considered by committee due to the presence of commercial arrangements for comparators and subsequent treatments and differences in modelling preferences.

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 sections 1b and 2c, there are no peri-adjuvant treatments in established clinical practice available for the treatment of early-stage NSCLC. 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 population, 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.
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. Cancer Research UK. Lung cancer. Last accessed: 19 Feb 2024. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/about. 2. National Lung Cancer Audit. 2023. National Lung Cancer Audit (NLCA) – State of the nation report 2023 for patients in England during 2021 and Wales during 2020-2021. . Last accessed: 19 Feb 2024. Available from: https://www.lungcanceraudit.org.uk/content/uploads/2023/04/NLCA-State-of-the-Nation-2023-Version-3-November-2023-1.pdf. 3. 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: 11 October 2023]. 4. Cancer Research UK. Cancer incidence statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence [Access Date: 11 October 2023].

5. Cancer Research UK. Lung cancer mortality statistics. Last accessed: 21 Mar 2024. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/mortality#ref-4.
6. NHS Digital. 2023. Cancer Survival in England, cancers diagnosed 2016 to 2020, followed up to 2021. Last accessed: 19 Feb 2024. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-survival-in-england/cancers-diagnosed-2016-to-2020-followed-up-to-2021.
7. Birring SS, Peake MD. Symptoms and the early diagnosis of lung cancer. *Thorax* 2005;60(4):268-9.
8. NHS. 2022. Diagnosis: lung cancer. Last accessed: 19 Feb 2024. Available from: https://www.nhs.uk/conditions/lung-cancer/diagnosis/.
9. National Institute for Health and Care Excellence. 2023. NICE guideline [NG122]. Lung cancer: diagnosis and management. Full guideline (2011). Last accessed: 20 Feb 2024. Available from: https://www.nice.org.uk/guidance/NG122.
10. National Institute for Health and Care Excellence. 2023. TA876 - Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer. Last accessed: 20 Feb 2024. Available from: https://www.nice.org.uk/guidance/ta876.
11. National Institute for Health and Care Excellence. 2022. TA823 - Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer. Last accessed: 20 Feb 2024. Available from: https://www.nice.org.uk/guidance/ta823.
12. National Institute for Health and Care Excellence. 2022. TA761 - Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection. Last accessed: 20 Feb 2024. Available from: https://www.nice.org.uk/guidance/ta761.
13. 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.
14. 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.
15. Cancer Research UK. 2023. About side effects of chemotherapy. Last accessed: 21 Mar 2024. Available from: https://www.cancerresearchuk.org/about-cancer/treatment/chemotherapy/side-effects/about.
16. Cancer Research UK. 2023. Chemotherapy for lung cancer. Last accessed: 21 Mar 2024. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/treatment/chemotherapy-treatment.
17. 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.
18. 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* 2024;33(4):1409-20.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID5094]

Clarification questions

May 2024

File name	Version	Contains confidential information	Date
NICE ID5094 Pembrolizumab peri-adjuvant NSCLC – Response to CQs [CON]	1.0	**Yes**	13 May 2024

Notes for external assessment groups (EAGs) and NICE

[TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

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

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

Section A: Clarification on effectiveness data

A1. Priority question.

a) In CS, Appendix D (p52), it is stated that "The following competing survival distributions were considered using the multivariate NMA framework: Weibull, Gompertz, log-logistic, and second order fractional polynomials including p1=-1, -0.5, 0, 0.5 or 1 and p2= -1, -0.5, 0, 0.5 or 1". Please provide justification for

conducting NMAs using the chosen survival distributions and the chosen values for powers p1 and p2.

b) It is stated (CS, Appendix D, p52) that, "for the relative treatment effects in the second order fractional polynomial framework, we assessed models which assume: (1) treatment only has an impact on two of the three parameters describing the hazard function over time (i.e., one scale and one shape parameter), and (2) treatment has an impact on all three parameters describing the hazard function over time (i.e., one scale and two shape parameters)." The EAG notes that analyses were undertaken for investigator-assessed EFS and BICR EFS, using both random-effects and fixed-effects models. Please provide:

1. **a complete list of all analyses that were undertaken to conduct time-varying HR NMAs**

2. **a detailed explanation (considering both model fit statistics and plausibility of reported HRs) of how the best-fitting model was chosen for i) investigator-assessed EFS and ii) BICR EFS**

MSD note that the text quoted from appendix D contained an error and should have stated "Weibull, Gompertz, and second order fractional polynomials including p1=0 or 1 and p2= -1, -0.5, 0, 0.5 or 1." The company apologise for the error. As described below, the second order fractional polynomials allow hazard functions that emulate the log-logistic distribution.

The competing survival distributions considered using the multivariate network meta-analysis (NMA) framework were: Weibull, Gompertz, and second order fractional polynomials including p1=0 or 1 and p2= –1, –0.5, 0, 0.5 or 1. In essence, the second order fractional polynomial models are extensions of the Weibull and Gompertz model and allow arc- and bathtub shaped hazard functions, which emulate parametric distributions such as log normal and log-logistic but offer additional flexibility due to the higher number of parameters.

Fixed effects analyses were conducted using each of the 22 models listed below, which covers a wide range models with a variety of fits. Powers of 2 and 3, while theoretically feasible, were not examined because the resulting squared or cubed time transformations typically result in parameters close to zero. The company notes that the options examined are in line with, or

more extensive than, the range of models explored in fractional polynomial-NMAs judged as appropriate and correctly implemented by the EAG in previous NICE submissions.[1-4] Second order p1=0 or 1 fractional polynomials are, respectively, Weibull and Gompertz distributions with an additional time component for more flexibility.

In relation to the economic model, it is worth noting that fractional polynomial models are extremely flexible and the effect of the time-varying NMA only affects how well the economic model mirrors data that have been observed or are expected to be observed in the near term, that is, between study follow-up and the imposition of the cure assumption. The company's view is that the wide range of options examined sufficiently covers the range of plausible outcomes and mirrors the observed data well, while providing clinically reasonable near-term projections for use within the economic model (see Figure 1).

The candidate options were:-

- Weibull family;
  - Scale, 1st shape;
    - P1= 0;
    - P1= 0, P2= –1;
    - P1= 0, P2= –0.5;
    - P1= 0, P2= 0;
    - P1= 0, P2= 0.5;
    - P1= 0, P2 =1.
  - Scale, 2nd shape;
    - P1= 0, P2= –1;
    - P1= 0, P2= –0.5;
    - P1= 0, P2= 0;
    - P1= 0, P2= 0.5;
    - P1= 0, P2= 1.

- Gompertz family;
  - Scale, 1st shape;
    - P1= 1;
    - P1= 1, P2= –1;
    - P1= 1, P2= –0.5;
    - P1= 1, P2= 0;
    - P1= 1, P2= 0.5;
    - P1= 1, P2= 1.
  - Scale, 2nd shape;
    - P1= 1, P2= –1;

- P1= 1, P2= –0.5;
- P1= 1, P2= 0;
- P1= 1, P2= 0.5;
- P1= 1, P2= 1.

Analyses using the first order models and the six second order models with the lowest fixed effects deviance information criterion (DIC) were then conducted using random effects models. Selection of the best-fitting fixed effects and random effects models were based on lowest DIC. The model fit statistics for investigator-assessed (IA) and blinded-independent central review (BICR)-assessed event-free-survival (EFS) in the intention-to-treat (ITT) population are provided in Table 1 and Table 2, respectively. Visual inspection of the modelled survival curves fitted to the trial level reported Kaplan–Meier curves was carried out to confirm that extrapolations in the lowest DIC models were plausible.

The company note that DIC statistics are uniformly lower in the fixed effects models compared with the random effects models and that statistical heterogeneity in the network arises from the chemotherapy+surgery versus surgery comparison, which is informed by multiple studies. The consistently lower DIC for fixed effects models suggests these models are the most appropriate for decision-making on the effectiveness of pembrolizumab over time versus other options within the network.

Table 1. DIC for alternative fractional polynomial NMA models — Investigator-assessed EFS (ITT population)

Distribution	Model	Scenario	Deviance	pD	DIC	RE Deviance	RE pD	RE DIC
Weibull family	P1=0	scale, 1st shape	817.8	15.8	833.7	818.6	16.7	835.4
	P1=0, P2=-1		680.8	20.7	701.5	--	--	--
	P1=0, P2=-0.5		673.2	20.3	693.6	674.2	21.4	695.6
	P1=0, P2=0		670.3	21	691.3	671	21.9	693
	P1=0, P2=0.5		676.9	21	697.9	677.5	22.2	699.7
	P1=0, P2=1		689.7	21	710.7	--	--	--
	P1=0, P2=-1	scale, 2nd shape	674.3	20.4	694.7	--	--	--
	P1=0, P2=-0.5		670.5	20.1	690.6	671.2	21.3	692.6
	P1=0, P2=0		672.4	21.1	693.5	673.2	21.9	695.1
	P1=0, P2=0.5		678.2	21	699.2	--	--	--
	P1=0, P2=1		691.2	20.9	712.1	--	--	--
Gompertz family	P1=1	scale, 1st shape	716.1	16.1	732.2	717	17	734
	P1=1, P2=-1		676.8	21.1	698	--	--	--
	P1=1, P2=-0.5		682.7	20.9	703.7	--	--	--
	P1=1, P2=0		691.1	20.9	712	--	--	--

	P1=1, P2=0.5		699.7	21	720.7	--	--	--
	P1=1, P2=1		706.9	20.7	727.6	--	--	--
	P1=1, P2=-1	scale, 2nd shape	670.8	20.8	691.6	671.4	21.9	693.3
	P1=1, P2=-0.5		678.8	20.9	699.7	--	--	--
	P1=1, P2=0		689.6	21.1	710.7	--	--	--
	P1=1, P2=0.5		699.3	21.1	720.5	--	--	--
	P1=1, P2=1		706.9	20.9	727.8	--	--	--

Highlighted cell indicates the lowest DIC.
Abbreviations: DIC, deviance information criterion; ITT, intent-to-treat; NMA, network-meta-analyses; RE, random effects.

Table 2. DIC for alternative fractional polynomial NMA models — BICR-assessed EFS (ITT population)

Distribution	Model	Scenario	Deviance	pD	DIC	RE Deviance	RE pD	RE DIC
Weibull family	P1=0	scale, 1st shape	828.9	15.8	844.7	829.5	17	846.5
	P1=0, P2=-1		682.3	20.7	702.9	--	--	--
	P1=0, P2=-0.5		670.8	20.3	691	--	--	--
	P1=0, P2=0		663.6	20.9	684.5	664.3	22.1	686.4
	P1=0, P2=0.5		667.6	21	688.6	668.2	22	690.2
	P1=0, P2=1		679.8	21	700.8	--	--	--
	P1=0, P2=-1	scale, 2nd shape	675.9	20.4	696.2	--	--	--
	P1=0, P2=-0.5		668.3	20	688.2	669	21	690.1
	P1=0, P2=0		665.3	21	686.3	666.1	22.1	688.2
	P1=0, P2=0.5		668.5	21	689.5	--	--	--
	P1=0, P2=1		680.3	20.9	701.2	--	--	--
Gompertz family	P1=1	scale, 1st shape	721.5	16	737.5	722.4	17.1	739.5
	P1=1, P2=-1		669.2	21.1	690.3	670.1	22	692.1
	P1=1, P2=-0.5		672.9	20.8	693.7	--	--	--
	P1=1, P2=0		680.5	20.9	701.4	--	--	--
	P1=1, P2=0.5		690.3	21.1	711.4	--	--	--
	P1=1, P2=1		700.2	20.8	721	--	--	--
	P1=1, P2=-1	scale, 2nd shape	664.1	20.7	684.8	664.8	21.8	686.5
	P1=1, P2=-0.5		669.9	20.8	690.7	--	--	--
	P1=1, P2=0		679.7	21	700.7	--	--	--
	P1=1, P2=0.5		690.3	21.1	711.3	--	--	--
	P1=1, P2=1		700.1	20.8	720.9	--	--	--

Highlighted cell indicates the lowest DIC.
Abbreviations: DIC, deviance information criterion; ITT, intent-to-treat; NMA, network-meta-analyses; RE, random effects.

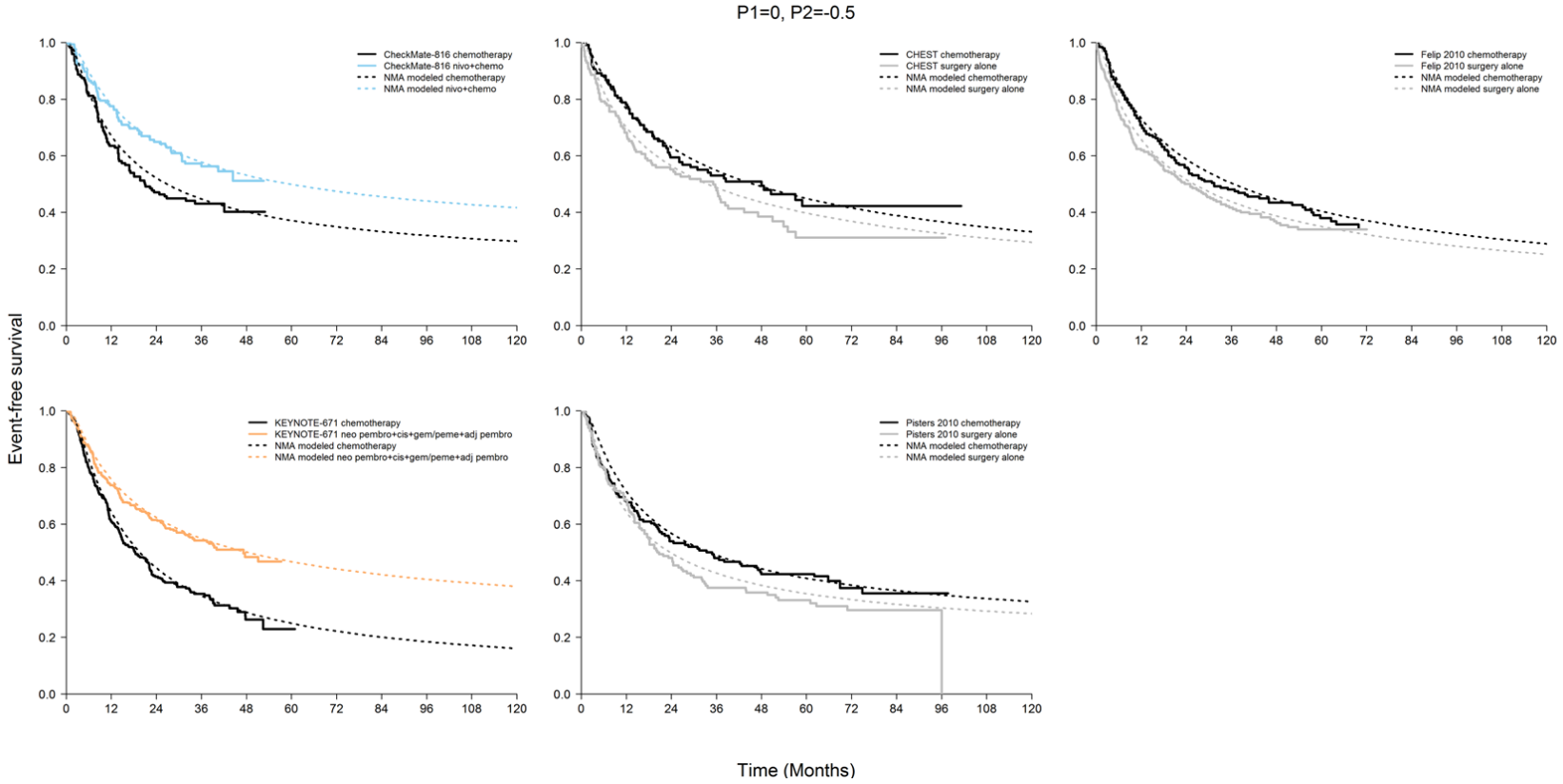
The company notes that the base-case NMA produces curves with a good visual fit to the observed EFS KM curves from the trials within the network (see Figure 1), bearing in mind that the pooled estimates from the NMA are only expected to fit the three individual trials within the chemotherapy versus surgery comparison approximately. The best fitting Gompertz curve,

which was used in scenario analysis is presented in Figure 2. The Weibull curve was chosen in the base case as it had the best statistical fit.

Scenario analyses were conducted where the hazard ratio from the NMA was held constant at the time maximum follow up from KEYNOTE-671 (5.2 years) and these scenarios had no impact on QALYs gained, indicating that random fluctuations were unlikely to be present or had limited impact on results due to the imposition of a cure assumption at 5–7 years.

Figure 1. Results of fractional polynomial model for EFS (investigator-assessed); survival curves overlayed with KM validation check (P1=0, P2=-0.5; scale and 2nd shape) (Weibull); ITT population (A: fixed effects, B: random effects)

A)



B

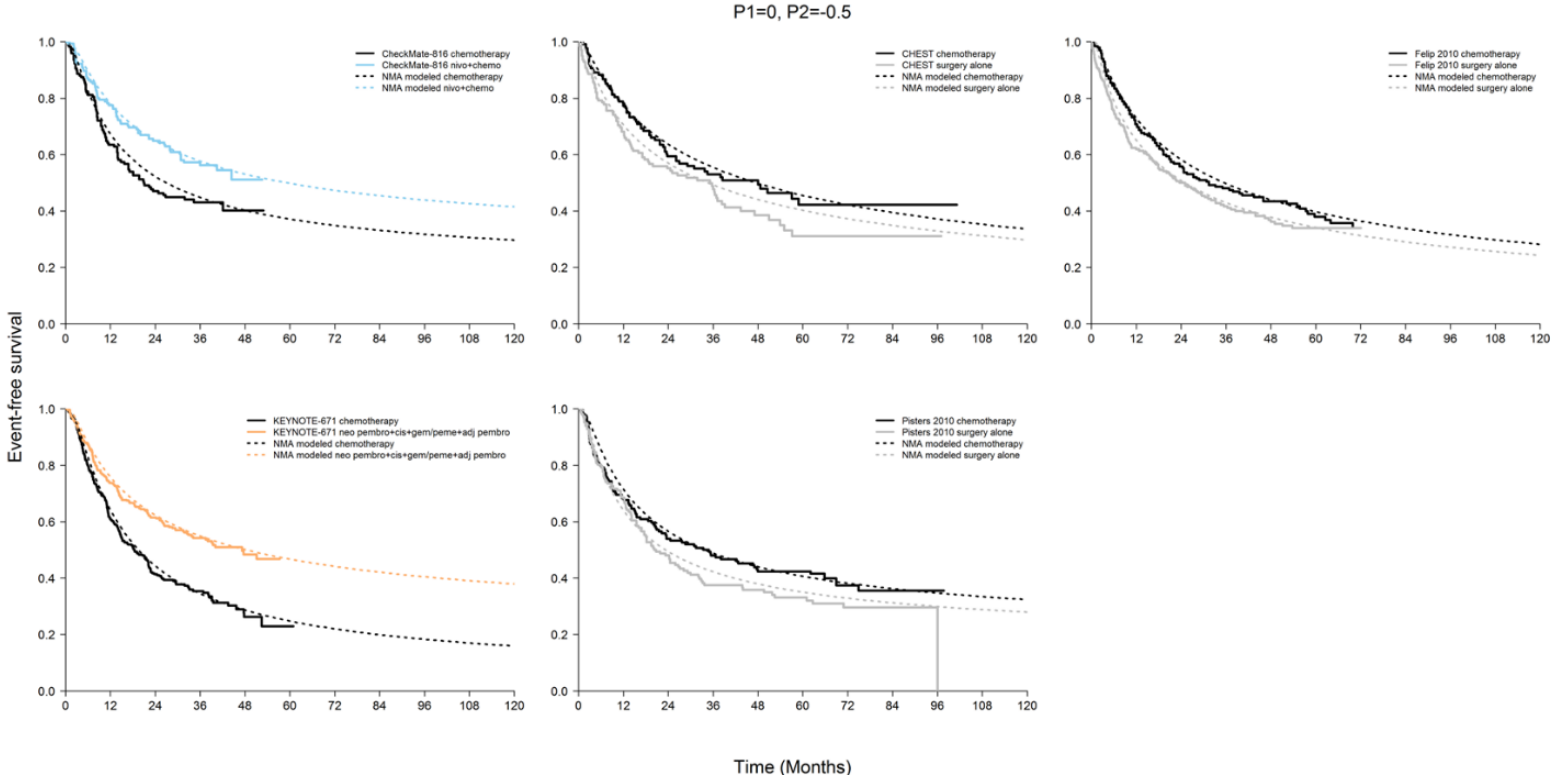
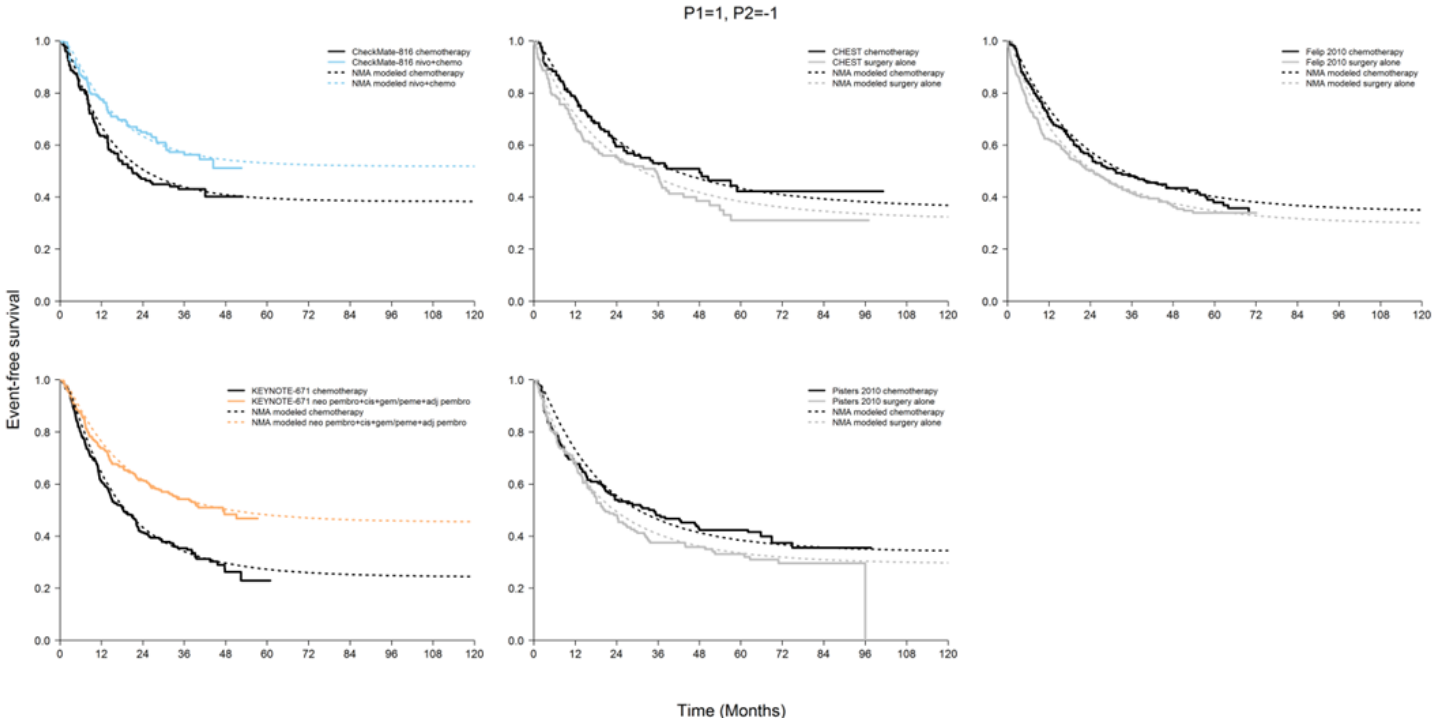
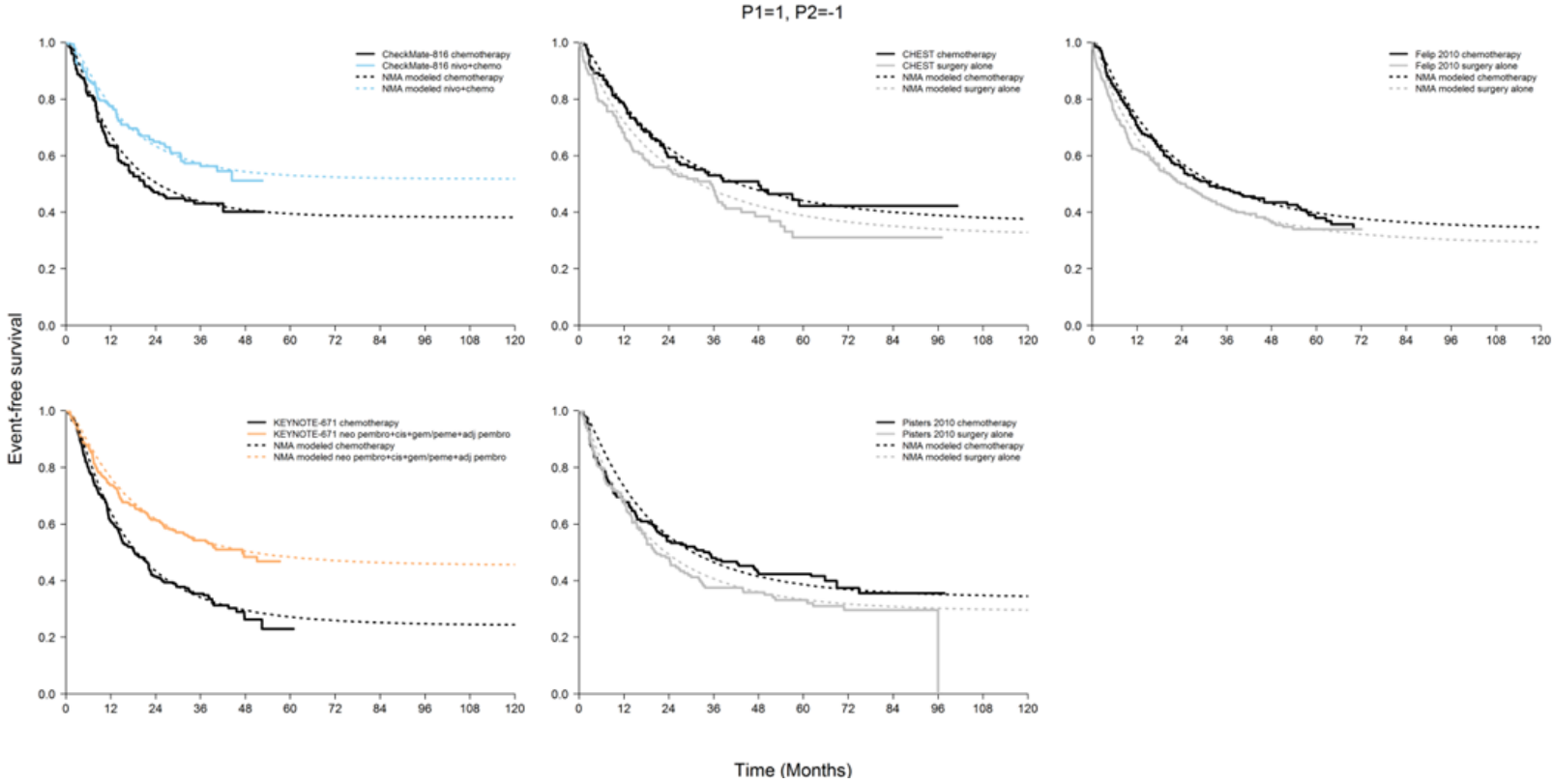

P1=0, P2=-0.5
Event-free survival
Time (Months)
CheckMate-816 chemotherapy
CheckMate-816 nivo+chemo
NMA modeled chemotherapy
NMA modeled nivo+chemo
CHEST chemotherapy
CHEST surgery alone
NMA modeled chemotherapy
NMA modeled surgery alone
Felip 2010 chemotherapy
Felip 2010 surgery alone
NMA modeled chemotherapy
NMA modeled surgery alone
KEYNOTE-671 chemotherapy
KEYNOTE-671 neo pembro+cis+gem/peme+adj pembro
NMA modeled chemotherapy
NMA modeled neo pembro+cis+gem/peme+adj pembro
Pisters 2010 chemotherapy
Pisters 2010 surgery alone
NMA modeled chemotherapy
NMA modeled surgery alone

Figure 2. Results of fractional polynomial model for EFS (investigator-assessed); survival curves overlayed with KM validation check (P1=1, P2=-1; scale and 2nd shape) (Gompertz); ITT population (A: fixed effects, B: random effects)



B)


P1=1, P2=-1
Event-free survival
Time (Months)
CheckMate-816 chemotherapy
CheckMate-816 nivo+chemo
NMA modeled chemotherapy
NMA modeled nivo+chemo
CHEST chemotherapy
CHEST surgery alone
NMA modeled chemotherapy
NMA modeled surgery alone
Felip 2010 chemotherapy
Felip 2010 surgery alone
NMA modeled chemotherapy
NMA modeled surgery alone
KEYNOTE-671 chemotherapy
KEYNOTE-671 neo pembro+cis+gem/peme+adj pembro
NMA modeled chemotherapy
NMA modeled neo pembro+cis+gem/peme+adj pembro
Pisters 2010 chemotherapy
Pisters 2010 surgery alone
NMA modeled chemotherapy
NMA modeled surgery alone

A2. Please provide justification for not performing NMAs for the following outcomes: pCR, AEs, HRQoL.

Pathological complete response (pCR), adverse events (AEs) and health-related quality of life (HRQoL) were not pre-specified endpoints of interest in the protocol for the NMA because these outcomes would not inform the analysis of cost-effectiveness and would not be implemented in the economic model.

After carrying out a feasibility assessment, it was determined that it would not be feasible to conduct NMAs of HRQoL or AEs due to limitations in the data available across the network, differences in outcome definitions, and differences in the timepoint of assessments. HRQoL outcomes were sparsely reported across the included trials. The only common HRQoL measure available in two or more trials was EQ-5D, which was reported in both KEYNOTE-671 (EQ-5D-5L) and CheckMate 816 (EQ-5D-3L). However, differing timepoints of the follow-up assessments between the trials precluded carrying out a credible indirect comparison.

In terms of AEs, only KEYNOTE-671 and CheckMate 816 used Common Terminology Criteria for Adverse Events (CTCAE) version 4 to grade safety outcomes; the other trials used earlier versions or did not report the version of CTCAE used to assess AEs. KEYNOTE-671 used MedDRA v26.0 to code AEs, whereas CheckMate 816 used MedDRA v24.0. KEYNOTE-671 included non-serious AEs up to 30 days after last treatment (which included both neoadjuvant and adjuvant therapy) and SAEs up to 90 days after last treatment, whereas CheckMate 816 included AEs and SAEs up to 30 days after neoadjuvant therapy (some patients also received adjuvant therapy).

pCR was reported in five trials (CheckMate 816, CHEST, Felip 2010, KEYNOTE-671, Pisters 2010), but was obviously only available for the chemotherapy arm in the chemotherapy versus surgery trials (CHEST, Felip 2010, Pisters 2010), so relative pCR could not be assessed in these studies. The company consider that, while an indirect treatment comparison (ITC) of the outcome of pCR is technically feasible, it would have a relatively small impact on HTA decision making because pCR is essentially a predictive surrogate outcome akin to “Complete Response” (CR) and “Partial Response” (PR) in metastatic trials. In metastatic trials, HTA decisions are not typically based on comparisons of surrogate outcomes when final outcomes (e.g., PFS and OS) are available. The company consider that there is relatively long follow-up on EFS (and, contextually, OS) in the trials in the network and that, while pCR was an important

predictor of efficacy during the initial publications and regulatory assessments associated with the trials in the network, that efficacy has now been observed. It can be seen from the figures detailing EFS by pCR status in the CS that not achieving a pCR is only very weakly predictive of having a recurrence. While achieving a pCR is a reasonably good predictor of not having a recurrence, around 15% of patients in both immunotherapy trials have recurred. It is also important to consider that, at present, event-free patients who either have or do not achieve pCR experience no difference in HRQoL or treatment decision. Furthermore, indirect comparisons of pCR do not have the ability to affect the ICERs from the economic model.

A3. In CS, Appendix D (p53), the company outlines the algorithm (proposed by Jansen 2011[5]) used to generate datasets from Kaplan-Meier curves for the comparator trials that were used in the NMAs.

1. Please clarify whether the Jansen algorithm was also used to generate the dataset used in the analysis presented in CS, Appendix D.3 (Figure 13).

2. Please provide justification for not using the more advanced Guyot method[6] for generating pseudo-IPD from Kaplan-Meier curves.

The company can confirm that the algorithm proposed by Guyot et al. was used to generate pseudo-IPD from the Kaplan–Meier curves. From the generated IPD, the Jansen algorithm was used to create discrete hazards in the form of number of events and number at risk at monthly intervals over time, which were then used as the inputs for the time-varying HR NMAs.

A4. Please clarify, for all NMAs, whether CheckMate 816 trial EFS data were adjusted or unadjusted for adjuvant therapy.

The reference to the HR and accompanying 95% CI for EFS from CheckMate 816 informing the NMAs is incorrect in the company submission. MSD apologise for the error. The source for the HR for EFS is Forde 2023,[7] which is a conference abstract. It is unclear from the details provided in the conference abstract whether the HR is adjusted or unadjusted for adjuvant chemotherapy.

A5. For the time-constant HR and time-varying HR NMAs, please confirm whether the posterior distribution of the between study heterogeneity indicated whether between study heterogeneity had been adequately estimated.

The posterior distribution of the heterogeneity parameter was stable and meaningfully different from the non-informative prior for all random effects NMAs conducted, indicating that it was adequately estimated.

There were three direct comparisons within the NMA. Two of these comparisons were informed by only one study so had no between-study heterogeneity and one comparison was informed by three studies. MSD consider that random effects evidence syntheses are often informed by pooling as few as three studies but are mindful of the advice in NICE TSD3; "*We must, however, repeat the important warning given in TSD2 (Section 6.2) that the posterior for the between trial standard deviation is likely to be extremely sensitive to the prior, and in particular that our "default" practice of using vague priors is likely to result in posteriors which allow for unrealistically high levels of heterogeneity. This will inevitably occur whenever the number of trials is small, or when the majority of trials are small*."[8]

Estimates of heterogeneity from the posterior distributions are presented in Table 3. MSD note that the credible intervals are relatively wide in all of the NMAs and reiterate that the fixed effects analysis is likely the most appropriate for decision-making.

Table 3. Estimates of heterogeneity parameter

Scenario	Heterogeneity parameter	
	Estimate	95% CrI
Constant HR		
IA-EFS, ITT	0.22	0.01 to 2.62
BICR-EFS, ITT	0.22	0.01 to 2.61
Time-varying HR		
IA-EFS, ITT		
P1=0, P2=-0.5 scale and 2nd shape (Weibull)	0.15	0.01 to 1.41
P1=1, P2=-1, scale, 2nd shape (Gompertz)	0.14	0.01 to 1.22
BICR-EFS, ITT		
P1=0, P2=0, scale and 1st shape	0.15	0.01 to 1.44

A6. Please provide the results of proportional hazards assessments for all trials included in the NMAs.

The proportional hazards assessments for all trials included in the NMAs are presented below. Pisters 2010 and Felip 2010 may have violated the proportional hazards assumption as the Grambsch and Therneau test and the Wald test p-values were less than 0.05 (Table 4). Therefore, an NMA involving these trials under the assumptions of constant hazards may be inappropriate. As noted in the CS, although formal proportional hazards violation tests are not significant for KEYNOTE-671 and Checkmate-816, that is a very high bar to meet, and there is a general trend towards respective divergence and convergence of hazards between the arms in these trials.

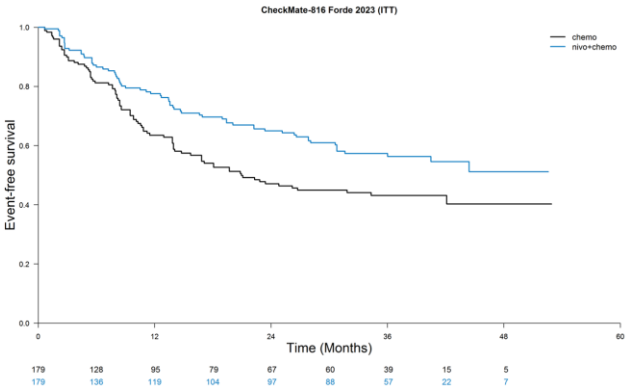
Table 4. Results of tests for violation of proportional hazards

Trial	Treatment comparison	Outcome	Grambsch & Therneau test, p-value	Wald test, p-value
CheckMate-816	nivo vs. chemo	EFS	0.4009	0.3741
CHEST	chemo vs. surgery	PFS	0.4913	0.3351
Felip 2010	chemo vs. surgery	DFS	0.0316	0.0124
KEYNOTE-671	pembro vs. chemo	EFS (IA)	0.1356	0.1273
		EFS (BICR)	0.2276	0.2174
Pisters 2010	chemo vs. surgery	PFS	0.0173	0.0109

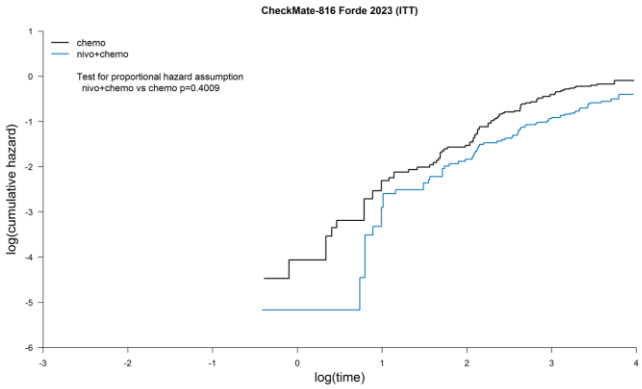
P-values less than 0.05 (highlighted) indicate violation of the proportional hazards assumption.
Abbreviations: BICR, blinded independent central review; chemo, chemotherapy; DFS, disease-free survival; EFS, event-free survival; IA, investigator-assessed; nivo, nivolumab; pembro, pembrolizumab; PFS, progression-free survival.

Figure 3. Proportional hazards test plots for EFS; CheckMate 816, ITT population

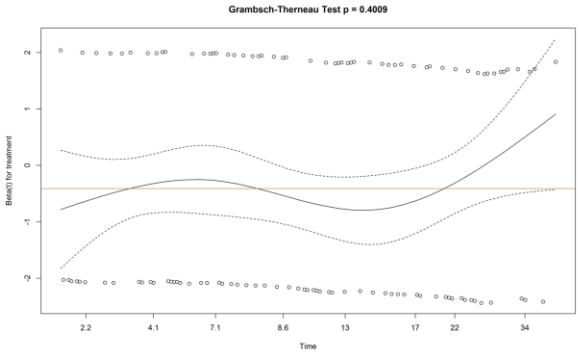
A) Kaplan-Meier



C) Log-cumulative hazard



B) Schoenfeld residuals



D) Smoothed hazard

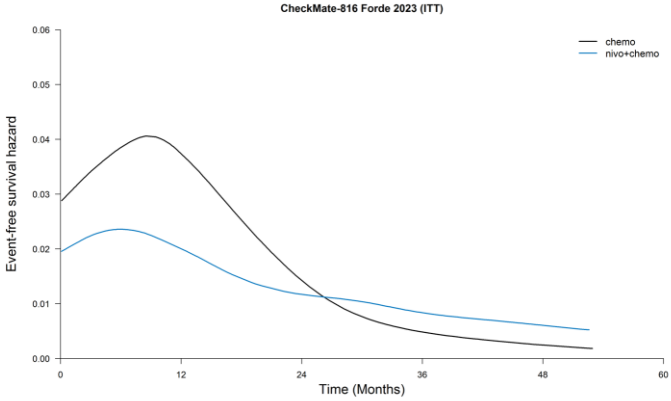
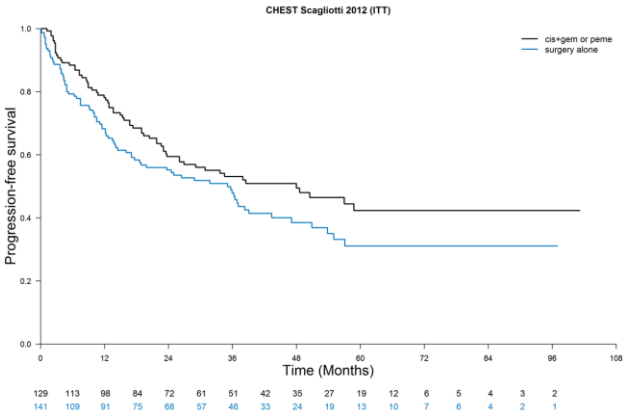
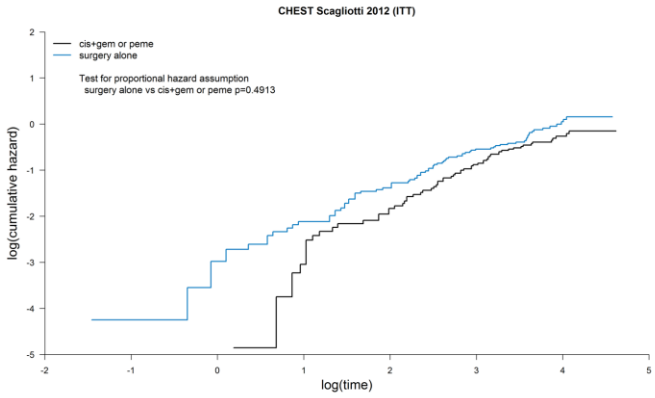


Figure 4. Proportional hazards test plots for PFS; CHEST, ITT population

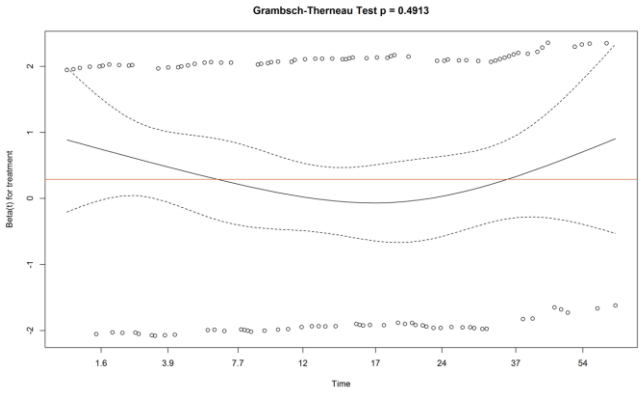
A) Kaplan-Meier



C) Log-cumulative hazard



B) Schoenfeld residuals



D) Smoothed hazard

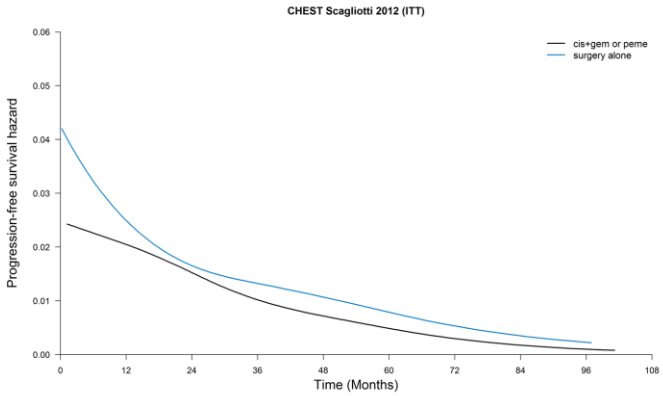
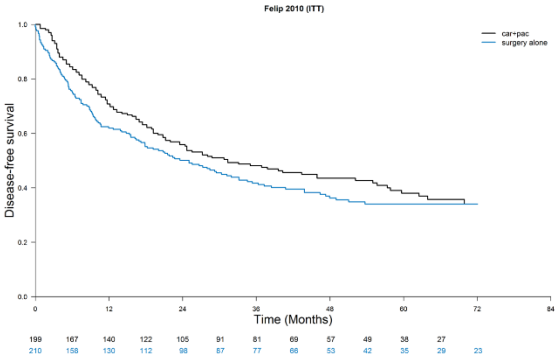
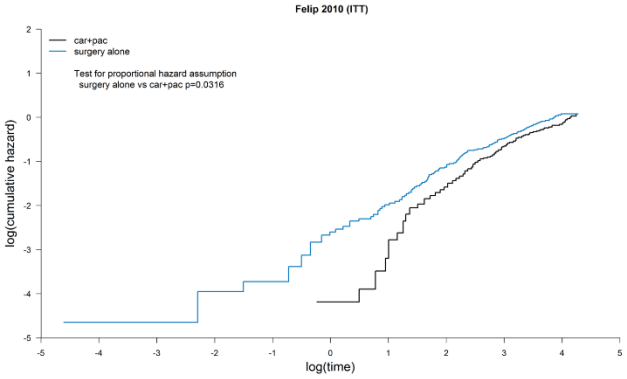


Figure 5. Proportional hazards test plots for DFS; Felip 2010, ITT population

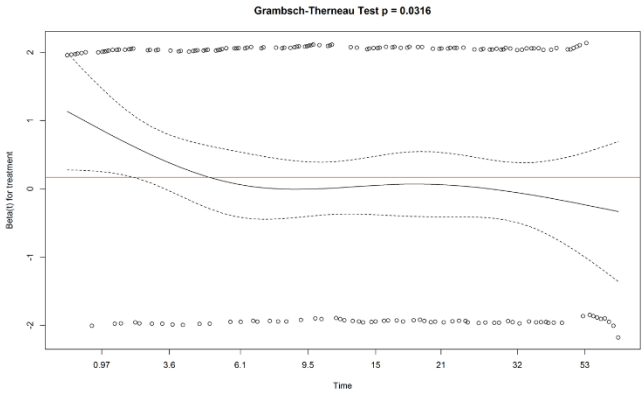
A) Kaplan-Meier



C) Log-cumulative hazard



B) Schoenfeld residuals



D) Smoothed hazard

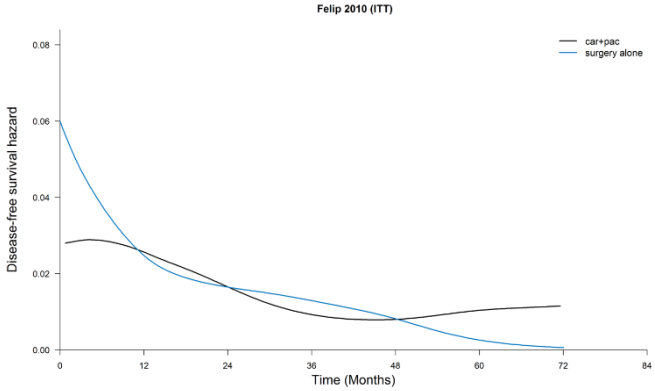
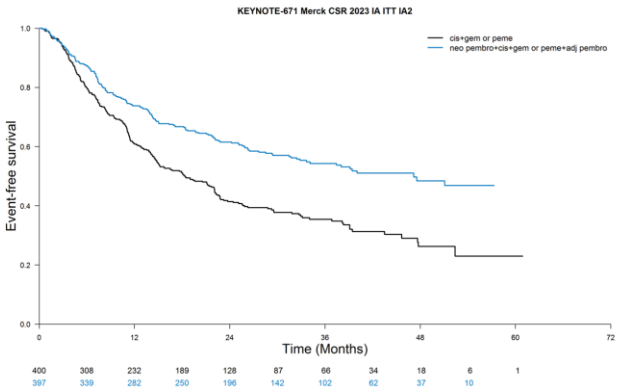
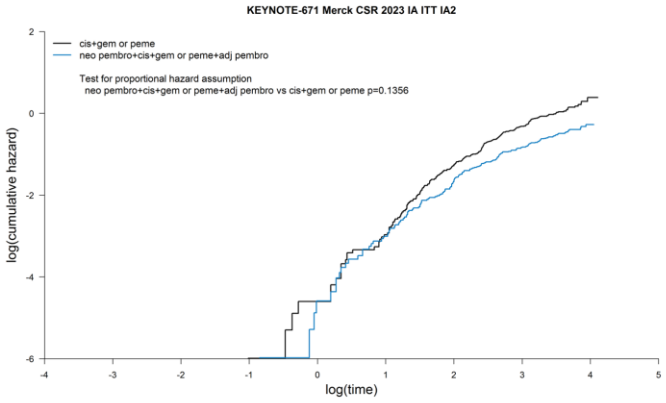


Figure 6. Proportional hazards test plots for EFS (investigator-assessed); KEYNOTE-671, ITT population

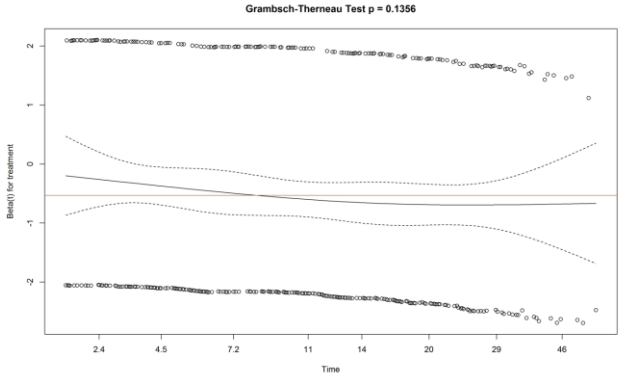
A) Kaplan-Meier



C) Log-cumulative hazard



B) Schoenfeld residuals



D) Smoothed hazard

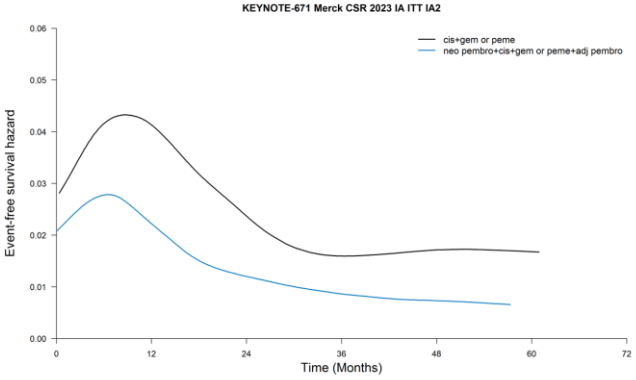
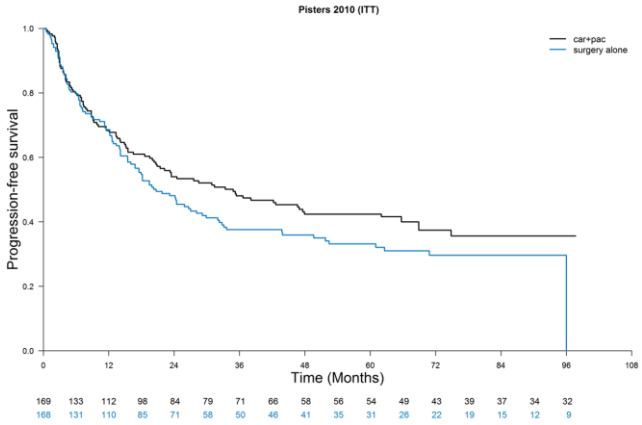
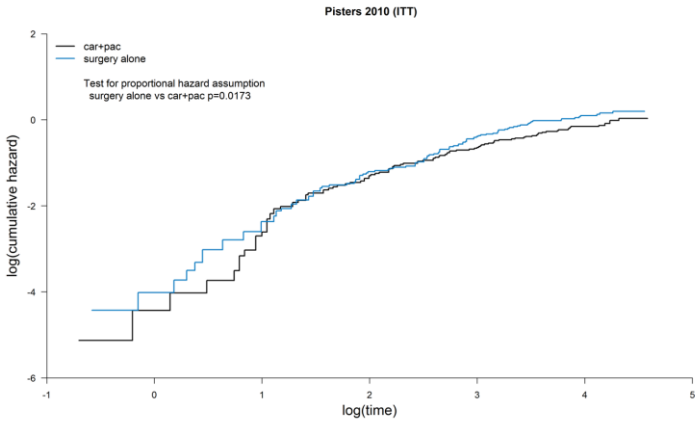


Figure 7. Proportional hazards test plots for PFS; Pisters 2010, ITT population

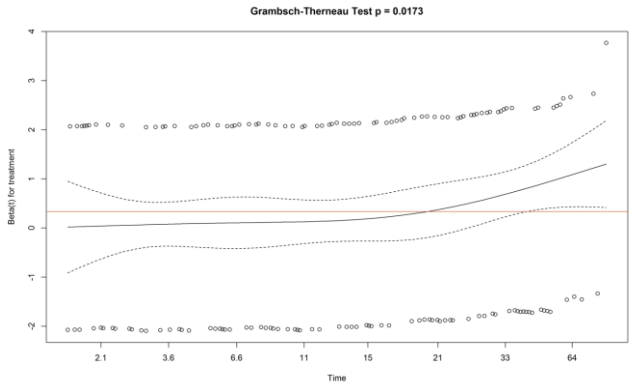
A) Kaplan-Meier



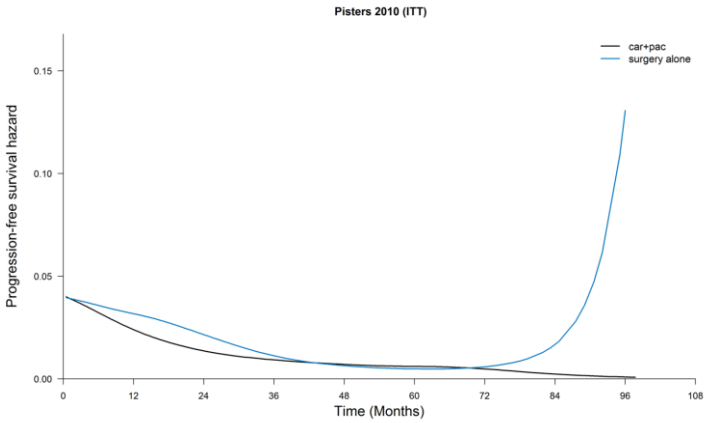
C) Log-cumulative hazard



B) Schoenfeld residuals



D) Smoothed hazard



Section B: Clarification on cost effectiveness data

B1. Priority question. Please clarify why adjuvant chemotherapy has not been included as a comparator in the economic model. If health outcomes and costs are assumed to be equivalent for patients receiving either neoadjuvant or adjuvant chemotherapy, please present evidence supporting this assumption.

When compared to the decision to initiate neo-adjuvant therapy, the decision to provide adjuvant therapy is distal in the treatment pathway and would only be initiated in a select group of those under consideration in this decision problem. MSD consider that, were adjuvant chemotherapy modelled, it would not be as a true comparator but more appropriately as a downstream treatment applying to some patients who achieve an R0 resection at surgery and then elect to have it. This is reflected in the approach to modelling

the neoadjuvant nivolumab plus chemotherapy arm. 12% of patients in CM816 received adjuvant chemotherapy. The costs of adjuvant therapy were included in the model based on this proportion of patients, thus capturing the health outcomes and costs of adjuvant chemotherapy.

In contrast adjuvant chemotherapy is not captured in the surgery alone arm of the model because patients in the trials used to inform efficacy in the NMA did not include adjuvant chemotherapy, with the exception of Felip (2018), where there was no statistically significant difference in DFS for surgery + adjuvant chemotherapy versus surgery alone. MSD consider that the impact of this omission is minimal due to clinical advice received by the company that adjuvant chemotherapy offers only a modest clinical benefit versus surgery alone. Based on clinical advice received by MSD prior to the 2022 Advisory Board,[9] approximately 50% of patients in the UK setting would receive adjuvant chemotherapy. However, during the discussion, one clinical advisor cited evidence from a 15-month single centre audit where approximately 30% of patients with who had surgery were considered eligible to receive adjuvant chemotherapy and approximately 30% of those eligible received it. This indicates that clinical practice may be variable and there is some uncertainty around the proportion of patients who receive adjuvant chemotherapy. Based on the modest clinical benefit and 50% or less of patients in the surgery alone arm receiving adjuvant chemotherapy, any underestimation of costs and health outcomes in this arm is likely to be minimal. Therefore, the inclusion of adjuvant chemotherapy would not change the conclusion that pembrolizumab plus chemotherapy is cost-effective when compared to surgery alone, especially given the magnitude of Net Health Benefit generated by pembrolizumab versus surgery alone.

Additionally, in TA876 (which included adjuvant chemotherapy as a comparator) nivolumab plus chemotherapy had a lower ICER when compared with adjuvant chemotherapy than when compared to surgery alone in the EAG base case and was dominant in the company base case:

- Company base case:
    - versus surgery alone: £2,685 per QALY gained
    - versus adjuvant chemotherapy: dominant
- EAG base case
    - versus surgery alone: £3,478

- versus adjuvant chemotherapy: £879

It is therefore possible that, were adjuvant chemotherapy a comparator, it would result in improved cost-effectiveness of pembrolizumab when contrasted with the comparison to surgery alone. The corollary of the data presented above are also that the surgery+adjuvant chemotherapy strategy must be at least "extendedly dominated" by the combination of surgery alone and neoadjuvant nivolumab in both the company's and EAG's base case analyses in TA876. The reason for this is that the addition of adjuvant chemotherapy generates more QALYs than surgery alone, so sits to the right of it on the cost-effectiveness plane, but the ICER is higher for nivolumab versus surgery. If nivolumab is considered a comparator, and the company can see no reason why it wouldn't be, then we believe that adjuvant chemotherapy cannot be considered a recommendable option anyway as it does not sit on the Cost-effectiveness Acceptability Frontier (CEAF).

B2. Please provide the average numbers of cycles of adjuvant pembrolizumab received by patients who did and did not have a pCR following surgery (in a format similar to CS, Table 57).

The proportion of patients who received each cycle of pembrolizumab in the adjuvant phase by pCR status is reported in Table 5 below.

Table 5. Proportion of patients receiving each cycle of adjuvant treatment by pCR status

Cycle	Patients with pCR, n (%)	Patients without pCR, n (%)
Participants in adjuvant phase	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]

B3. Please provide (in a format similar to CS, Table 16), breakdowns, for patients in each arm of the KEYNOTE-671 trial, of progression-recurrence events into local-regional recurrence events and distant metastases events.

Please see Table 6 below:

Table 6. Analysis of event-free survival based on investigator assessment

Outcome	Pembrolizumab[a] (N=397)	Placebo[a] (N=400)
Type of first event in EFS analysis (n) (%)		
No event	223 (56.2)	152 (38.0)
Event	174 (43.8)	248 (62.0)
Locoregional progression or locoregional recurrence	66 (16.6)	111 (27.8)
Distant metastasis	57 (14.4)	95 (23.8)
Death	50 (12.6)	40 (10.0)[e]
Unknown[b]	1 (0.3)	2 (0.5)

[a] Treatment regimen abbreviated. Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab, where placebo refers to the same treatment plan with placebo substituted for pembrolizumab.
[b] LP/LR vs DM assessment not available
Database cutoff date of 10 July 2023.

B4. The company explains that when selecting the base case parametric distributions to model transitions from the EF state, the transition to the death state was evaluated first as it had the fewest number of events in the KEYNOTE-671 trial (CS, p112). Please justify why 'fewest number of events' was an appropriate reason for prioritising the evaluation of this parameter.

Ultimately, the sequence of steps in our selection process did not affect the final choice of base-case distribution. The selected base-case combination (Generalized Gamma/Generalized Gamma/Log-normal under Approach #1) was the #1 best-fitting of the original 397 candidate combinations in the neoadjuvant chemotherapy arm, and the #5 best-fitting of the 397 in the perioperative pembrolizumab arm (see B40:H436 on 'Param Output – part 1' tab in the model). As fit in the neoadjuvant chemotherapy arm was typically poorer (i.e., higher MSEs) than in the pembrolizumab arm, this arm was prioritised in the selection process to minimise the overall uncertainty.

To identify the most appropriate base-case combination of distributions among 397 candidate combinations, our process selects the distribution of EF→Death first for expediency, but ultimately places greater emphasis on the choice of distributions EF→LR/P and EF→DM. Of the three transitions exiting the EF state (i.e., EF→LR/P, EF→DM,

EF→Death), the EF→Death transition is the least frequent and therefore has relatively limited influence on the EFS curve, as well as limited influence as a competing risk on the other two transitions exiting EF. The choice of distribution for the cause-specific hazards of EF→Death is therefore less critical than the choice of distributions for the cause-specific hazards of EF→LR/P and EF→DM. In both arms, seven of the top 10 best-fitting combinations among the original 397 candidate combinations used Generalized Gamma for both EF→LR/P and EF→DM combined with a different distribution of EF→Death − implying that the EF→Death distribution was of relatively little consequence to the overall fit between observed and predicted EFS, while the optimal choice of distributions for EF→LR/P and EF→DM is far more important. A scenario with an alternative distribution for EF→Death (Generalized gamma, the best-fitting overall distribution in the pembrolizumab arm) was tested in a scenario analysis which demonstrated a very small impact on the ICER compared with the base case.

Our process to select base-case distributions for these three transitions was therefore designed to rapidly select the distribution of EF→Death based on summarized fit statistics, which reduces the number of candidate combinations of distributions from 397 to 67 in a single step. The next several steps in the process then gradually identify the most suitable distributions for the cause-specific hazards of EF→LR/P and EF→DM, based on a close inspection of statistical fit and visual fit, and clinical plausibility, among the 67 remaining combinations.

B5. Of the 43 patients identified as having a local-regional recurrence/progression in the SEER Medicare dataset, please provide information about the treatments these patients received after diagnosis of a local-regional recurrence/progression.

In the SEER-Medicare study, locoregional (LR) events after the original surgery were identified based on either a diagnosis code of secondary malignancy in nearby lymph nodes, or the receipt of an LR treatment (which could consist of either another surgery, radiotherapy alone, or radiotherapy and chemotherapy).

One limitation of the SEER-Medicare analysis was the need to use claims-based indicators (e.g., subsequent surgeries, treatments, etc.) to assist in identifying recurrence type. This limitation also applies to determining the proportions of patients who received different LR treatments among those identified as having LR. In particular, there were no patients in the N=43 sample with chemotherapy alone as their LR treatment, as the use of systemic treatments without radiotherapy was treated as a claims-based indicator for DM (see Table 7). Therefore, patients who received chemotherapy alone were categorized as having a DM

rather than an LR event and are therefore not present in the N=43 sample. This may have contributed to the relatively high proportion of patients in the SEER-Medicare cohort who received surgery as their first LR treatment (i.e., because patients who received chemotherapy alone are not included in the LR sample).

The use of claims-based indicators for recurrence type is likely to result in some misclassification of LR/P as DM and vice versa, but this is a limitation of administrative claims data rather than a conceptual inconsistency in our health state definitions: The use of subsequent systemic treatment alone is a clear indicator of disease recurrence (either LR/P or DM), and categorizing such events as DM will result in correct classification of recurrence type more often than categorizing such events as LR/P. (All recurrence events identified in the real-world cohort must be categorized as LR/P or DM to align with our health states.) In the economic model, a minority of patients entering the LR/P state receive systemic treatment alone, whereas all patients entering the DM state are modelled to receive subsequent systemic treatment. The classification of such events as DM in the SEER-Medicare cohort is therefore generally well-aligned with the health state definitions in the model, allowing for some margin of error given the nature of claims data. We consider this an acceptable limitation given the limited data source options available for estimating transition probabilities from the LR/P state, and our consideration of various calibration approaches to adjust the transition probabilities from the LR/P and/or DM states.

The company notes that the economic model reproduces observed trial OS well, which gives some reassurance that the intermediate transition probabilities are generalisable.

Table 7. Distribution of Loco-Regional Recurrence Treatments

Drug	Count	Percent (N=43)
No LR Treatment Identified	[redacted]	[redacted]
Radio Monotherapy	[redacted]	[redacted]
Wedge Resection	[redacted]	[redacted]
Lobectomy	[redacted]	[redacted]
Pneumonectomy	[redacted]	[redacted]
Chemoradiotherapy	[redacted]	[redacted]

Abbreviations: LR, locoregional.

B6. Please remove the PAS discounts applied to comparator costs and present updated cost effectiveness results.

While conducting additional quality assurance MSD identified minor changes required to some model inputs. Details of these amendments and the impact on the ICER are presented in Table 8.

Table 8. Amendments to model inputs and impact on ICER

	Description of change	Impact on ICER? (Large, small, none)
1.	Changed the general population utility values from Ara et al. to Hernández Alava et al. 2022[10] (values from Health Survey for England 2013), as recommended by the DSU. The general population values from Ara et al. (2010)[11] are retained as a scenario (for results see Table 12 and can be selected in the model specification sheet.	Small decrease
2.	Updated an error in the CT scan resource use inputs to correctly reflect clinical advice received in 2023 advisory board. 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 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
3.	Corrected the cost of radiotherapy from £5,557 to £4,517. Correction based on clinical advice that the following assumptions are appropriate (previously the company had assumed an even split between radiotherapy options due to lack of evidence on what the split might be): No patients receive hyper fractionated RT, The split between standard fractionated radiotherapy and CHART is 95% and 5% respectively, Removing the 30 fraction regimen from the costs of standard fractionated radiotherapy	Small increase

Updated cost-effectiveness results removing comparator PAS discounts and incorporating the changes described in Table 8 are presented below.

Table 9. Updated base-case deterministic results (pembrolizumab at PAS price, comparators/subsequent treatments at list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus comparator (£/QALY)
Peri-adjuvant pembrolizumab	[redacted]	8.31	[redacted]	-	-	-	-
Neoadjuvant chemotherapy	[redacted]	6.17	[redacted]	[redacted]	2.14	1.93	[redacted]
Neoadjuvant nivolumab + chemotherapy	[redacted]	7.28	[redacted]	[redacted]	1.03	0.91	[redacted]
Surgery alone	[redacted]	5.28	[redacted]	[redacted]	3.04	2.66	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.
Incremental results are for pembrolizumab + chemotherapy versus the comparator technology.

Table 10. Fully incremental base case deterministic results

Fully incremental results	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus reference (£/QALY)
Surgery alone	[redacted]	5.28	[redacted]	Reference	Reference	Reference	Reference
Neoadjuvant nivolumab + chemotherapy	[redacted]	7.28	[redacted]	[redacted]	2.00	1.76	[redacted]
Peri-adjuvant pembrolizumab	[redacted]	8.31	[redacted]	[redacted]	1.03	2.66	[redacted]
Neoadjuvant chemotherapy	[redacted]	6.17	[redacted]	[redacted]	-2.14	0.73	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.
Fully incremental costs and QALYs are calculated using the least costly treatment arm as the reference arm. Fully incremental ICERs are calculated versus the next less expensive treatment that is not dominated or extendedly dominated

Table 11. Probabilistic cost-effectiveness results (mean of 1,000 iterations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab + chemotherapy vs:							
Pembrolizumab + chemotherapy	[redacted]	**8.20**	[redacted]	-	-	-	-
Neoadjuvant chemotherapy	[redacted]	6.17	[redacted]	[redacted]	2.03	1.84	[redacted]
Neoadjuvant nivolumab + chemotherapy	[redacted]	7.21	[redacted]	[redacted]	0.99	0.86	[redacted]
Surgery alone	[redacted]	5.16	[redacted]	[redacted]	4.17	2.66	[redacted]

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

The probabilistic results are very similar to those in the deterministic base case. The PSA results demonstrate that, under base case assumptions, there is a [redacted]% probability that peri-adjuvant treatment with pembrolizumab is a cost-effective treatment strategy versus chemotherapy or surgery alone and a [redacted]% probability that it is cost-effective versus nivolumab at list price at a threshold of £30,000/QALY gained. There was an 85% probability that peri-adjuvant pembrolizumab generated more QALYs than neoadjuvant nivolumab. The company notes that this table corrects an error in Table 72 of the submission where the values total LYG and total QALYs for the comparator regimens were transposed.

Figure 8. PSA scatterplots

A) Pembrolizumab vs neoadjuvant chemotherapy

B) Pembrolizumab vs neoadjuvant nivolumab

C) Pembrolizumab vs surgery alone

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 9. Cost-effectiveness acceptability curve

Figure 10. Tornado diagram featuring top 10 individually influential parameters

A) Pembrolizumab vs neoadjuvant chemotherapy (presented as incremental net monetary benefit as pembrolizumab is dominant in all but 1 scenario)

B) Pembrolizumab vs neoadjuvant nivolumab

C) Pembrolizumab vs surgery alone

Abbreviations: CI, confidence interval; DM, distant metastases; EF, event-free; ICER, incremental cost-effectiveness ratio; IV, intravenous; LR, loco-regional recurrence or progression; QALY, quality-adjusted life year.

Table 12. Scenario analyses

#	Scenario	Description	Vs chemotherapy			Vs nivolumab			Vs surgery		
			Δ Costs (£)	Δ QALY	ICER (£/QALY)	Δ Costs (£)	Δ QALY	ICER (£/QALY)	Δ Costs (£)	Δ QALY	ICER (£/QALY)
-	**Base case**	**-**	[redacted]	**1.93**	[redacted]	[redacted]	**0.91**	[redacted]	[redacted]	**2.66**	[redacted]
1	Alternative functions for modelling of transitions from EF state (Approach #1; EFàLR/P, EFàDM, EFàdeath)	Alternative EFàdeath distribution Gen gamma/ Gen gamma/ Gen gamma	[redacted]	2.12	[redacted]	[redacted]	0.85	[redacted]	[redacted]	2.68	[redacted]
2		2nd best-fitting in chemo arm Gompertz/ Gen gamma/ Log-normal	[redacted]	1.89	[redacted]	[redacted]	0.87	[redacted]	[redacted]	2.67	[redacted]
3		2nd best-fitting in pembro arm Gen gamma/ Gompertz/ Log-normal	[redacted]	2.05	[redacted]	[redacted]	0.84	[redacted]	[redacted]	2.68	[redacted]
4	Alternative approaches for modelling transitions from EF state	Approach #2 (time-constant HR): Gompertz/ Gompertz/ Gompertz	[redacted]	1.73	[redacted]	[redacted]	0.89	[redacted]	[redacted]	2.64	[redacted]
5		Approach #3 (time-varying HR): Gompertz/ Gompertz/ Gompertz	[redacted]	1.95	[redacted]	[redacted]	0.85	[redacted]	[redacted]	2.67	[redacted]
6	Alternative cure assumptions	Cure period 3-5 years (95% of patients cured at 5 years)	[redacted]	1.89	[redacted]	[redacted]	0.73	[redacted]	[redacted]	2.67	[redacted]
7		Cure period 5-10 years (95% of patients cured at 10 years)	[redacted]	1.95	[redacted]	[redacted]	0.96	[redacted]	[redacted]	2.66	[redacted]
8		Cure period 7-10 years (95% of patients cured at 10 years)	[redacted]	1.94	[redacted]	[redacted]	1.00	[redacted]	[redacted]	2.64	[redacted]
9		100% patients cured at end of 5-7 year cure period	[redacted]	1.93	[redacted]	[redacted]	0.90	[redacted]	[redacted]	2.67	[redacted]
10	Time-varying HR NMA for external comparators: Alternative assumptions	Time-varying HR vs pembrolizumab not held constant after end of trial	[redacted]	1.93	[redacted]	[redacted]	0.91	[redacted]	[redacted]	2.66	[redacted]
11		Time-varying HR vs pembrolizumab trends to 1 at 5-7 years	[redacted]	1.93	[redacted]	[redacted]	0.87	[redacted]	[redacted]	2.63	[redacted]
12		Time-varying HR vs pembrolizumab not held constant after end of trial + Cure period 7-10 years	[redacted]	1.94	[redacted]	[redacted]	1.01	[redacted]	[redacted]	2.64	[redacted]

13		Time-varying HR vs pembrolizumab trends to 1 at 5-7 years + Cure period 7-10 years	[redacted]	1.94	[redacted]	[redacted]	0.84	[redacted]	[redacted]	2.51	[redacted]
14		Weibull random-effects time-varying HR NMA	[redacted]	1.93	[redacted]	[redacted]	0.92	[redacted]	[redacted]	2.70	[redacted]
15		Gompertz fixed-effects time-varying HR NMA	[redacted]	1.93	[redacted]	[redacted]	0.68	[redacted]	[redacted]	2.64	[redacted]
16		Gompertz random-effects time-varying HR NMA	[redacted]	1.93	[redacted]	[redacted]	0.69	[redacted]	[redacted]	2.69	[redacted]
17	Time-constant HR NMA for external comparators	Time-constant EFS HRs for nivolumab and surgery vs pembrolizumab	[redacted]	1.93	[redacted]	[redacted]	0.49	[redacted]	[redacted]	2.43	[redacted]
18		Time-constant EFS HRs for nivolumab and surgery vs pembrolizumab + Cure period 3-5 years	[redacted]	1.89	[redacted]	[redacted]	0.47	[redacted]	[redacted]	2.43	[redacted]
19		Time-constant EFS HRs for nivolumab and surgery vs pembrolizumab + Cure period 7-10 years	[redacted]	1.94	[redacted]	[redacted]	0.50	[redacted]	[redacted]	2.42	[redacted]
20	Adjustment factor for transitions from DM	No adjustment of DMàdeath transitions based on SEER Medicare	[redacted]	1.91	[redacted]	[redacted]	0.90	[redacted]	[redacted]	2.64	[redacted]
21	Calibration of downstream transitions to observed OS	LR/Pàdeath transitions temporarily calibrated over maximum trial follow-up (i.e. 5 years) to achieve better fit to observed OS	[redacted]	2.10	[redacted]	[redacted]	0.93	[redacted]	[redacted]	2.81	[redacted]
22		LR/PàDM and LR/Pàdeath transitions temporarily calibrated over maximum trial follow-up (i.e. 5 years) to achieve better fit to observed OS	[redacted]	2.13	[redacted]	[redacted]	0.91	[redacted]	[redacted]	2.81	[redacted]
23		Transitions from LR/P and DM states temporarily calibrated over maximum trial follow-up (i.e. 5 years) to achieve better fit to observed OS	[redacted]	2.09	[redacted]	[redacted]	0.92	[redacted]	[redacted]	2.80	[redacted]
24	pCR stopping rule	Patients who are identified at surgery as having achieved pCR are assumed not to receive adjuvant pembrolizumab	[redacted]	1.93	[redacted]	[redacted]	0.91	[redacted]	[redacted]	2.66	[redacted]

25		pCR stopping rule + Gompertz fixed-effects time-varying HR NMA	[redacted]	1.93	[redacted]	[redacted]	0.68	[redacted]	[redacted]	2.64	[redacted]
26		pCR stopping rule + Time-constant HR NMA	[redacted]	1.93	[redacted]	[redacted]	0.49	[redacted]	[redacted]	2.43	[redacted]
27	Alternative market shares of systemic therapy in the DM state	20% of patients assumed not to receive active 1L treatment for NSCLC (see Appendix M.3.2)	[redacted]	2.00	[redacted]	[redacted]	0.93	[redacted]	[redacted]	2.72	[redacted]
28	Alternative sources of utility values	EF utility from KEYNOTE-671 includes Grade 1-2 AEs (0.830)	[redacted]	1.78	[redacted]	[redacted]	0.84	[redacted]	[redacted]	2.48	[redacted]
29		Post-progression DM utility from KEYNOTE-671 (0.727)	[redacted]	1.91	[redacted]	[redacted]	0.90	[redacted]	[redacted]	2.65	[redacted]
30		General population utilities from Ara 2010	[redacted]	1.91	[redacted]	[redacted]	0.90	[redacted]	[redacted]	2.64	[redacted]
31	Alternative dosing schedule for pembrolizumab	Pembrolizumab dosing schedule 200 mg Q3W in adjuvant setting	[redacted]	1.93	[redacted]	[redacted]	0.91	[redacted]	[redacted]	2.66	[redacted]
32	Pessimistic composite scenario 1	○ Gompertz fixed-effects time-varying HR NMA ○ Time-varying HR vs pembrolizumab trends to 1 at 5-7 years ○ Cure period 7-10 years ○ 20% patients do not receive 1L DM treatment ○ EF utility includes Grade 1-2 AEs ○ Q3W dosing in adjuvant setting	[redacted]	1.86	[redacted]	[redacted]	0.60	[redacted]	[redacted]	2.37	[redacted]
33	Pessimistic composite scenario 2	○ 31 + pCR stopping rule	[redacted]	1.86	[redacted]	[redacted]	0.60	[redacted]	[redacted]	2.37	[redacted]

Abbreviations: AE, adverse event; DM, distant metastases; EF, event-free; EFS, event-free survival; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LR/P, locoregional recurrence or progression; NMA, network meta-analysis; NSCLC, non-small-cell lung cancer; OS, overall survival; pCR, pathological complete response; QALY, quality-adjusted life year; QxW, every x weeks.

Disaggregated results of the base-case analysis are presented below.

Table 13. Summary of QALY gain by health state

Health state	Total QALYs				Incremental QALYs, pembrolizumab vs:		
	Peri-adjuvant pembrolizumab	Neoadjuvant chemotherapy	Neoadjuvant nivolumab	Surgery alone	Neoadjuvant chemotherapy	Neoadjuvant nivolumab	Surgery alone
EF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LR/P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastases; EF, event-free; LR/P, locoregional recurrence or progression; QALY, quality-adjusted life year.

Table 14. Summary of costs by health state

Health state	Total costs (£)				Incremental costs (£), pembrolizumab vs:		
	Peri-adjuvant pembrolizumab	Neoadjuvant chemotherapy	Neoadjuvant nivolumab	Surgery alone	Neoadjuvant chemotherapy	Neoadjuvant nivolumab	Surgery alone
EF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LR/P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastases; EF, event-free; LR/P, locoregional recurrence or progression; QALY, quality-adjusted life year.

Table 15. Summary of predicted resource use by category of cost

Health state	Total costs (£)				Incremental costs (£), pembrolizumab vs:		
	Peri-adjuvant pembrolizumab	Neoadjuvant chemotherapy	Neoadjuvant nivolumab	Surgery alone	Neoadjuvant chemotherapy	Neoadjuvant nivolumab	Surgery alone
Neoadjuvant/adjuvant treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoadjuvant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjuvant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoadjuvant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adjuvant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initial surgery and radiotherapy costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initial surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in LR/P state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Salvage surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in DM state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LR/P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastases; EF, event-free; LR/P, locoregional recurrence or progression.

B7. Perioperative durvalumab (ID6220) is listed as a comparator on the scope subject to NICE appraisal and may be recommended into routine commissioning before the perioperative pembrolizumab committee meeting. Please include perioperative durvalumab in the economic modelling or provide clinical expert opinion to justify that its exclusion on the basis that it will not be established clinical practice, even if recommended.

The company has not done this for several reasons:-

1. The NICE ACM1 to discuss peri-adjuvant durvalumab (9th July) is scheduled approximately one month before the ACM1 to discuss peri-adjuvant pembrolizumab (7th August). It is not possible that Technology Appraisal Guidance will be issued before this date and far from clear that a Final Draft Guidance document would be publicly available, even if durvalumab is recommended into baseline commissioning in one meeting and not into the Cancer Drugs Fund, like some other early NSCLC appraisals, which had a more mature publicly available evidence base (TA761, TA823) have been. From a process point of view, the company therefore consider it unlikely that durvalumab can reasonably be considered “established clinical practice” on the 7th August.

2. As noted at the clarification call between NICE, the company and the EAG, data have not been forthcoming from the pivotal durvalumab trial, AEGEAN, for some time. The data that were first presented in early 2023, based on 11.7 months of follow-up are the only data that are in the public domain. The company consider it possible that the NICE committee will be taking its decision based on more mature data than are currently publicly available. As noted in the CS, there is no standard economic model in early NSCLC and the manufacturer of durvalumab may be using a different economic model to MSD. This is not an MTA, and it is not clear by what process the clinical and economic evidence considered by NICE in July could reasonably be incorporated into a decision taken in August, were durvalumab recommended.

3. The company note that, as far as decision-making goes, the most important comparator of interest for peri-adjuvant durvalumab will likely be neoadjuvant nivolumab. The hazard ratio for the primary outcome (EFS) in the AEGEAN study was the same as was observed in the study which underpins nivolumab (both 0.68), CheckMate-816, despite CheckMate-816 including a maximum of three cycles of treatment and AEGEAN including a maximum of 16 cycles of treatment. This is important for several reasons. First, even if peri-adjuvant durvalumab achieves a

positive NICE recommendation it is not clear that a treatment with no better treatment effect and higher patient and service-related burden than the standard of care immunotherapy regimen would be considered desirable enough by clinicians and patients to be regarded as "established clinical practice", at least until more data are available. It is notable that no OS data are available and 11.7 months follow-up is relatively short compared to the other immunotherapy studies in early NSCLC (e.g. approximately 30 months in KEYNOTE-671). The next reason why this is important relates to the inclusion of durvalumab's ability to affect the decision on pembrolizumab. For the inclusion of durvalumab to change the committee's decision on pembrolizumab it would not just have to be a broadly cost-effective option but would have to be significantly more cost-effective than neoadjuvant nivolumab i.e. generate significant improvements in Net Health Benefit. Given the factors noted above, the company consider that to be an unlikely scenario.

4. If durvalumab achieves a baseline commissioning recommendation in July and an FDG is available by the 7th of August, the company suggest that the inclusion of durvalumab in decision-making can be handled in two ways. The company's preferred method would be for NICE to carefully take note of the committee's preferred assumptions and the likely base case Incremental Net Health Benefit for durvalumab versus nivolumab. If this Incremental Net Health Benefit is small, consistent with a base case ICER of approximately £20,000-£30,000/QALY gained (in one direction or the other), then it can be reasonably assumed that the inclusion of durvalumab does not materially affect the decision space. This is because the conclusion that pembrolizumab generates equal or better Net Health Benefit versus other comparators in the space, if that is the conclusion the committee would otherwise draw, would not be materially affected. The second option would be to consider the evidence on durvalumab qualitatively in the network of evidence presented for this appraisal; for the proportional hazards NMA the company notes that, based on the publicly available data, durvalumab's EFS HR implies it would be dominated by nivolumab were it included in the model. For the time-varying NMA, the company consider that 11.7 months of follow-up is too short to draw reliable conclusions about the treatment effect over time in AEGEAN. The company's view is that, taken together, the evidence on durvalumab being significantly more cost-effective than nivolumab is too uncertain to meaningfully affect the decision on the cost-effectiveness of peri-adjuvant pembrolizumab even if it manages to achieve a

positive recommendation to baseline commissioning in one meeting and an FDG is issued ahead of the 7th August.

B8. Adjuvant osimertinib (TA761) is currently in the CDF but has its exit appraisal committee meeting (ID5120) in June 2024 and it may be recommended before the perioperative pembrolizumab committee meeting. It is possible that osimertinib could be considered established practice very quickly after it's appraisal. Osimertinib is modelled as a first line treatment in the distant metastases health state in the model, implying that the population has a proportion of people with EGFR positive disease who would also be eligible for adjuvant osimertinib. Please include osimertinib as a comparator in the economic modelling.

The company agree it is likely that osimertinib will exit the CDF and become the standard of care for the adjuvant treatment of EGFR-positive patients who have undergone complete resection. However, this population is distal to the decision problem in this technology appraisal; only a subset of downstream patients in the surgery alone and chemotherapy+surgery arms of the model would receive adjuvant osimertinib. Osimertinib cannot therefore be considered a comparator but instead should be handled in one of two ways:-

1. Both EGFR testing and surgery +/- neoadjuvant chemotherapy followed by osimertinib may be considered to be standard care and it may therefore be that the population in this decision problem is only, in reality, EGFR-negative patients. Few patients in KEYNOTE-671 received an EGFR test, EGFR testing was not done in the surgery versus chemotherapy + surgery trials while Asian EGFR-negative patients were actively excluded from Checkmate-816 so analyses may not be reasonably adjusted for EGFR status. The company suggest that the analyses be considered generalisable to the EGFR-negative population with the caveats that were highlighted within the CS (section B.2.8.1.3.).

2. EGFR status may be considered to be unknown at the time of the radical treatment plan. In this case osimertinib can be considered to be a subsequent treatment in the surgery alone and chemotherapy + surgery arms of the model, applicable only to those who are EGFR positive and have a complete resection. Approximately 90% of patients based have a complete resection, based on feedback from a clinical advisory board).[9] Assuming, based on literature evidence, that 12-15% of patients are EGFR positive then 9%–13.5%[12, 13] of patients would be eligible for osimertinib in the surgery alone and chemotherapy + surgery arms. Given pembrolizumab is

highly cost-effective versus these comparators, the company consider it implausible that osimertinib when used in 9%–13.5% of patients could alter the Net Health Benefit of these strategies to such an extent that it would exceed the Net Health Benefit generated by pembrolizumab.

Section C: Textual clarification and additional points

C1. The company uses the term 'high risk of recurrence' in the CS. Please provide a definition of this term. Does the definition vary by stage of disease?

Selection criteria reported in the recently updated Summary of Product Characteristics for pembrolizumab define patients with resectable NSCLC who are at high risk of recurrence as those with:[14]

- Tumour size ≥4 cm; or
- Tumours of any size that are either accompanied by N1 or N2 status; or
- Tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or
- Tumours that involve the main bronchus <2 cm distal to the carina but without involvement of the carina; or
- Tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or
- Tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.

C2. How many independent reviewers were involved in the quality assessment of the trials included in the company NMAs?

Two independent reviewers conducted the quality assessments of the included trials. Any discrepancies between the two reviewers that could not be resolved through consensus were resolved by consulting a third reviewer.

C3. Please provide a copy of the company SLR protocol.

The protocol for the SLR is provided as part of the response to clarification questions.

C4. Please confirm the source of the CheckMate 816 trial Kaplan-Meier EFS data that were incorporated into the time-varying HR NMAs. The reference provided in CS, Appendix D (Table 13) appears to be incorrect.

MSD apologise for the error. The correct reference is Forde 2023,[7] which is freely available online.

Additional clarification

As noted in the response to question B6, MSD identified an error in the reporting of the PSA results in table 72 of the company submission. New redacted and confidential versions of the submission have been uploaded with this error corrected and should replace the original versions to ensure confidential information is correctly redacted.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID5094].

Patient Organisation Submission

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

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

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, work in lung cancer patient care (information, support and advocacy activity) and raise awareness of the disease and issues associated with it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment	**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 TA 876 approved Nivolumab (a different immunotherapy drug), with chemotherapy, for the neoadjuvant treatment of resectable nsclc (NICE TA876). There is a need to explore additional therapies in improving outcomes and reducing recurrence in this patient group.
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We note the results from the phase 3 KEYNOTE-671 trial, which demonstrated a significant event free survival benefit with the use of Pembrolizumab added to neo-adjuvant chemotherapy and as postsurgical adjuvant therapy in patients with early stage nsclc. Adverse events were as expected, based on known toxicity profiles of the individual therapies. Patient and carers would want the best outcome of chemoimmunotherapy. 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. It is important that, in administering neoadjuvant therapy, the window for successful surgery is not missed. Delays, whilst being assessed for and undergoing neoadjuvant treatment, have the potential for disease progression, making surgery not feasible. In this scenario, patients could have been treated with up-front surgery (+/- adjuvant treatment) and potentially curative therapy, had neoadjuvant therapy not been undertaken.

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.	• Neoadjuvant / adjuvant immunochemotherapy 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.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID5094]

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]/ [redacted](Steering Committee)
2. Name of organisation	British Thoracic Oncology Group
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	Sponsorship and Registration fees from the annual conference
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes Sponsorship BTOG 2023 £60,000 BTOG2024 £60,000
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 cure more patients with resectable early 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.)	Increased overall survival, increased pathological complete response rate, longer event free survival and increased major pathological response rate
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, many patients still relapse and die of disease despite reseation.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Neoadjuvant 3 cycles of chemoimmunotherapy (CHECKMATE816) followed by surgery
9a. Are any clinical guidelines used in the	Formal NICE guidelines have not been made for this indication as it is relatively new

treatment of the 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.)	The pathway is well defined on paper but in clinical practice there is wide variation. Neoadjuvant chemoimmunotherapy of for selected IIA-IIIB resectable NSCLC. The main area of concern is that unresectable patients might be “pushed” into this pathway away from what we would consider standard care (radical concurrent chemoradiotherapy)
9c. What impact would the technology have on the current pathway of care?	Potentially, save more lives. All the treatments within this protocol are already part of NHS pathways
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	yes
10a. How does healthcare resource use differ between the technology and current care?	Currently we give 3 cycles of chemoIO followed by surgery. This protocol is slightly different in that it is 3months of chemoIO preop and 9 months of just IO post op
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care within chemo units,
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil over current units

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes
11a. Do you expect the technology to increase length of life more than current care?	Yes. There is already an overall survival benefit
11b. Do you expect the technology to increase health-related quality of life more than current care?	Long term yes. Obviously there will be toxicities associated with the treatment while it is being delivered
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The trial excluded specific patients with mutations for which this treatment is not approropriate (EGFR/ALK). In practice I would also exclude ROS1 patients

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	All drugs and regimens are already in widespread NHS use. SO there are no implementation issues. I do feel a few months of neoadjuvant therapy does make planning surgery much easier for surgical departments.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No. After preop treatment a ct will be done before surgery. ALSO CT's will be done during the postoperative pathway to exclude recurrance
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. The main additional utility is incorporating the post operative component for which there is a suggestion of additional benefit esp in those not achieving a pCR (although this needs prospective validation).
16a. Is the technology a 'step-change' in the management of the condition?	It's a further improvement in where we are.

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, its affords a survival benefit
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?	The side effects are well recognised and I would not expect anything outside the SPC for the relevant drugs

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Improved pCR, MPR Longer EFS Longer OS (preliminary data)
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	There is an increasing body of evidence showing the pCR/MPR are surrogates of better outcomes. `EFS is already recognised as a surrorage for OS. This trial has positive preliminary OS data (HR 0.73)

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No although a systematic review would need to look at data releases from major international conference presentations (ASCO/AACR/WCLC/ESMO). All of these are peer reviewed.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA876 and TA823?	No
21. How do data on real-world experience compare with the trial data?	We don't fully know this but it is likelt that at BTOG 2024 some RWE might be presented on UK experience on the checkmate 816 experience.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
22b. Consider whether these issues are different from issues with current care and why.	N/A

Topic-specific questions

23. Further to question 9, 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?	Currently those receiving neoadjuvant chemoIO do not receive post op adjuvant therapies.
24. Is PD-L1 testing of carried out as part of routine practice for early or locally advanced stage NSCLC?	Yes
25. Could you comment on the size of the population who might not have neo-adjuvant treatment but who would go straight to surgery followed by an adjuvant treatment? (See pages 7-8 of consultation comments)	It is likely that most stage III patients will get neoadjuvant therapy. In my experience there is reluctance in some surgical centres to offer this to Stage II patients where pts go straight to surgery. This is a much debated area of practice and I think it is fair to say the UK community is still finding its way.

27. How would having an immunotherapy as part of neo-adjuvant and/or adjuvant treatment affect the treatment options should the cancer progress to advanced or metastatic disease? **How is rechallenge with immunotherapy currently offered in the NHS?**	Once a patient relapses they should have the ability to be offered all postiental advanced disease options are currently available. A degree of common sense would be required as a patient actively progressing on adjuvant immunotherapy is unlikely to benefit from immunotherapy incorporated into their first line metastatic therapy

Key messages

26. In up to 5 bullet points, please summarise the key messages of your submission.	• Novel addition of post op “adjuvant” immunotherapy • Overall survival benefit seen HR 0.74 • Significant improvments in pCR/MPR/EFS • Evidence that post op component might be improving outcomes in the non pCR patients over just neoadjuvant therapy •

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) for resectable non-small cell lung cancer [ID5094]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 165408

Completed 10th June 2024

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Contributions of authors

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervised the final report
Sam Bryning	Critical appraisal of the economic model
Marty Chaplin	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
James Mahon	Critical appraisal of the economic model
Yenal Dundar	Critical appraisal of the company search strategies
Ashley Marsden	Critical appraisal of the company submission
John Green	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
APaT	All Participants as Treated
BICR	Blinded independent central review
BSC	Best supportive care
CDF	Cancer Drugs Fund
CI	Confidence interval
CrI	Credible interval
CS	Company submission
DFS	Disease-free survival
DIC	Deviance Information Criterion
DM	Distant metastases
EAG	External Assessment Group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQoL-5 Dimensions
FAS	Full Analysis Set
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
ICER	Incremental cost effectiveness ratio
IO	Immunotherapy
ITT	Intention-to-treat
KEYNOTE-671	The key trial discussed in the company submission
KM	Kaplan-Meier
LS	Least squares
LY	Life years
LR/P	Local-regional recurrence or progression
LYG	Life year gained
MHRA	Medicines and Healthcare products Regulatory Agency
mPR	Major pathological response
MSE	Mean squared error
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
OS	Overall survival
pCR	Pathological complete response
PAS	Patient Access Scheme

PDC	Platinum doublet chemotherapy
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PRO	Patient reported outcomes
PSS	Personal Social Services
Q3W/Q6W	Every 3 weeks/every 6 weeks
QALY	Quality adjusted life year
QLQ-C30	Core Quality of Life Questionnaire
RCT	Randomised controlled trial
SLR	Systematic literature review
SEER	Surveillance, Epidemiology, and End Results programme
SMC	Scottish Medicines Consortium
TNM	Tumour Node Metastasis
ToT	Time on treatment
TPS	Tumour Proportion Score
UICC	Union for International Cancer Control

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.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Key cost effectiveness results are presented in Section 1.6.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of key issues

ID	Summary of issue	Report sections
Issue 1	Identification of relevant comparator treatments for this appraisal	Section 2.4.5
Issue 2	The extent to which the KEYNOTE-671 trial results are generalisable to NHS patients	Section 2.3 and Section 3.2.3
Issue 3	Absence of reliable indirect OS NMA results for the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy (the most relevant comparator)	Section 2.4.6
Issue 4	Time-varying HR EFS NMA results should not be used to draw conclusions about the relative effectiveness of periadjuvant pembrolizumab versus nivolumab with chemotherapy or versus surgery	Section 3.7.7
Issue 5	The company has provided insufficient evidence to support the application of the HRs generated at the end of the KEYNOTE-671 trial follow-up period for the remaining model time frame (31.7 years)	Section 6.5
Issue 6	The use of time-varying EFS HRs to compare the effectiveness of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy (or versus surgery) was not sufficiently justified by the company	Section 6.5
Issue 7	Company model mortality rate for patients who remain event-free for ≥5 years may be too low	Section 6.6

EFS=event-free survival; HR=hazard ratio; NMA=network meta-analysis; OS=overall survival

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and health-related quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained.

Company model generates cost effectiveness results for the comparison of periadjuvant pembrolizumab versus three comparators. The EAG revisions that have the biggest effect on company costs and QALYs are:

- HR of 1 applied to pembrolizumab EFS curve after 41.4 months and 64 months for comparisons versus neoadjuvant nivolumab with chemotherapy and versus surgery alone respectively
- time constant HRs (fixed-effects model) used to model EFS for patients treated with neoadjuvant nivolumab with chemotherapy or surgery alone
- risk factor applied to general population mortality rates for patients assumed to be cured after 5 years

The EAG also explored the impact on costs of QALYs by carrying out the following analyses

- no difference in EFS between periadjuvant pembrolizumab and neoadjuvant nivolumab with chemotherapy
- age- and sex-matched general population utility value used to represent HRQoL in the event-free health state

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Comparator treatments

Report section	Section 2.4.5
Description of issue and why the EAG has identified it as important	The company did not provide evidence for four of the comparators listed in the final scope issued by NICE. NICE agreed with the company that two of the comparator treatments (chemoradiotherapy and adjuvant atezolizumab) were not relevant comparators. At clarification, NICE asked the company to provide cost effectiveness evidence for the comparison of periadjuvant pembrolizumab versus periadjuvant durvalumab and versus adjuvant osimertinib. In the clarification response, the company outlined their reasons for not providing this evidence (durvalumab was under assessment by NICE and osimertinib was in the CDF) and made suggestions about how evidence for these treatments could be incorporated into the NICE process if these treatments were recommended by NICE for routine commissioning prior to the first NICE AC meeting for periadjuvant pembrolizumab.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Guidance from NICE to make it clear to companies (and EAGs) whether all comparators listed in the final scope issued by NICE that might be recommended by NICE for routine use in the NHS prior to the first NICE AC meeting for the intervention should be included in the CS as relevant comparators.

AC=Appraisal Committee; CDF=Cancer Drugs Fund; CS=company submission; NICE=National Institute for Health and Care Excellence

Issue 2 Generalisability of KEYNOTE-671 trial data to NHS practice

Report section	Section 2.3 and Section 3.2.3
Description of issue and why the EAG has identified it as important	Direct clinical effectiveness evidence is only available from the KEYNOTE-671 trial for the comparison of periadjuvant pembrolizumab versus neoadjuvant chemotherapy; clinical advice to the EAG is that neoadjuvant chemotherapy is rarely used in NHS practice. Clinical advice to the company was that treatment would likely be stopped for patients who achieve pCR after surgery. Therefore, the relevance of the trial results to NHS patients is uncertain. In addition, it is unclear how clinicians will determine which patients are likely to benefit most from post-surgery immunotherapy. Further, clinical advice to the EAG is that KEYNOTE-671 trial patients are considerably younger (mean=63.1 years) than NHS patients (average age of 70 years) and that older, less fit NHS patients may not be suitable for treatment with immunotherapy treatment.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Not known
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice on the generalisability of KEYNOTE-671 trial results to NHS practice

EAG=External Assessment Group

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 3 Limited comparative clinical effectiveness evidence

Report section	Section 2.4.6
Description of issue and why the EAG has identified it as important	Indirect evidence is only available for EFS. The immaturity of KEYNOTE-671 trial OS data means that it has not been possible for the company to generate reliable indirect OS NMA results for the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab (the most relevant comparator).
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Not known
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice about the long-term clinical effectiveness of periadjuvant pembrolizumab and comparator treatments.

EAG=External Assessment Group; EFS=event-free survival; NMA=network meta-analysis; OS=overall survival

Issue 4 Limitations of company time-varying HR EFS NMAs

Report section	Section 3.7.7
Description of issue and why the EAG has identified it as important	The EAG does not consider that the company has provided a sufficiently strong rationale to support the view that time-varying HR EFS NMAs are more informative than time-constant HR EFS NMAs. Further, the EAG has the following concerns about the company time-varying HR EFS NMAs: • the long-term biological plausibility of time-varying HRs is uncertain • reliability of results is uncertain due to the subjective nature of the model selection process • the width of the 95% CrIs around time-varying HR estimates remains approximately the same at all time points and doesn't reflect the number of patients providing data at each time point (which diminishes over time). The EAG therefore considers that it is not appropriate to infer statistical significance (or lack of statistical significance) from these CrIs Due to these issues, the EAG considers that time-varying HR EFS NMA results should not be used to draw conclusions about the relative effectiveness of periadjuvant pembrolizumab versus nivolumab with chemotherapy or versus surgery.
What alternative approach has the EAG suggested?	The EAG considers that time-constant HR EFS NMA results are more reliable than time-varying HR EFS NMA results.
What is the expected effect on the cost effectiveness estimates?	See Issue 6
What additional evidence or analyses might help to resolve this key issue?	None

CrI=credible interval; EAG=External Assessment Group; EFS=event-free survival; HR=hazard ratio; NMA=network meta-analysis

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 5 The company estimates of the relative effectiveness of treatment with periadjuvant pembrolizumab versus comparator treatments on event-free survival may be an over-estimate.

Report section	Section 6.5
Description of issue and why the EAG has identified it as important	In the company base case, time-varying HR (fixed-effects) EFS NMA results were applied to the KEYNOTE-671 trial periadjuvant pembrolizumab data to generate EFS estimates for patients treated with neoadjuvant nivolumab with chemotherapy and those treated with surgery alone; HRs were kept constant beyond the observed KEYNOTE-671 trial follow-up period. Company NMA results show that the surgery alone HR remained stable over time. However, for the comparison versus neoadjuvant nivolumab with chemotherapy, the last estimated HR was the most optimistic, (favouring periadjuvant pembrolizumab). The EAG considers that the company has provided insufficient evidence to apply the HR generated at the end of the KEYNOTE-671 trial follow-up period for the remaining model time frame (31.7 years)
What alternative approach has the EAG suggested?	When comparing the clinical effectiveness of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy and versus surgery alone, apply a HR of 1 to the periadjuvant pembrolizumab EFS curve after 41.4 months and 64 months respectively.
What is the expected effect on the cost effectiveness estimates?	For the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy, the deterministic ICER per QALY increases by [redacted] to [redacted]. For the comparison of periadjuvant pembrolizumab versus surgery alone, the deterministic ICER per QALY increases by [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; EFS=event-free survival; HR=hazard ratio; ICER=incremental cost effectiveness ratio; NMA=network meta-analysis; QALY=quality adjusted life year gained

Issue 6 Company time-varying HR EFS NMA results should not be used to compare the clinical effectiveness of periadjuvant pembrolizumab versus comparator treatments

Report section	Section 6.5
Description of issue and why the EAG has identified it as important	The EAG considers that the use of time-varying EFS HRs to compare the effectiveness of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy (or versus surgery) was not sufficiently justified by the company. Further, the EAG does not consider that it is appropriate to infer statistical significance (or lack of statistical significance) from time-varying HR NMA 95% CrIs. The EAG considers that time-varying HR EFS NMA results do not provide robust statistical evidence to support a hypothesis that EFS HRs change over time.
What alternative approach has the EAG suggested?	Use constant HR (fixed-effects) EFS NMA results to estimate EFS for patients treated with neoadjuvant nivolumab with chemotherapy and patients treated with surgery alone.
What is the expected effect on the cost effectiveness estimates?	For the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy the deterministic ICER per QALY increases by [redacted] to [redacted]. For the comparison of periadjuvant pembrolizumab versus surgery alone, the deterministic ICER per QALY increases by [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	None

CrI=credible interval; EAG=External Assessment Group; EFS=event-free survival; HR=hazard ratio; ICER=incremental cost effectiveness ratio; NMA=network meta-analysis; QALY=quality adjusted life year gained

Issue 7 Company model mortality rate for patients who remain event-free for ≥5 years may be too low

Report section	Section 6.6
Description of issue and why the EAG has identified it as important	In the company model, a proportion (95%) of patients who remain event-free at 5 years are assumed to be cured such that the probability of progression to the LR/P or DM health states for these patients is zero by year 7, and the probability of death is equal to general population mortality by year 7. Evidence from the literature suggests that patients alive after 5 years may experience long-term excess mortality due to the increased risk of a second cancer diagnosis.
What alternative approach has the EAG suggested?	Based on data reported in the literature, the EAG has adjusted the model mortality rate for patients assumed to be cured after 5 years so that it is higher than the general population mortality rate.
What is the expected effect on the cost effectiveness estimates?	For the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy the deterministic ICER per QALY increases by [redacted] to [redacted]. For the comparison of periadjuvant pembrolizumab versus surgery alone, the deterministic ICER per QALY increases by [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice.

DM=distant metastases; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; LR/P=local-regional recurrence/progression; QALY=quality adjusted life year gained

1.6 Summary of EAG's alternative ICERs per QALY gained

Summary deterministic cost effectiveness results are presented in Table B and C and probabilistic fully incremental results are presented in Tables D and E. Cost effectiveness results for the comparison of periadjuvant pembrolizumab versus neoadjuvant chemotherapy are presented in Appendix 8.3.

Table B Deterministic pairwise results (periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy), PAS price for pembrolizumab and list prices for all other treatments

Scenario/EAG revisions	Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs		
A. Company clarification base case	[redacted]	**0.906**	[redacted]	-
R1) HR of one applied to pembrolizumab EFS curve after 41.4 months	[redacted]	0.537	[redacted]	[redacted]
R2) Time-constant EFS HR (fixed-effects model)	[redacted]	0.492	[redacted]	[redacted]
R3) Risk factor applied to general population mortality rates for patients assumed to be cured after 5 years	[redacted]	0.795	[redacted]	[redacted]
B. EAG preferred scenario (R1-R3)	[redacted]	**0.360**	[redacted]	[redacted]
C. EAG exploratory scenarios				
C1. No difference in EFS between periadjuvant pembrolizumab and neoadjuvant nivolumab	[redacted]	-0.052	[redacted]	-
C2. Age- and sex-matched general population utility value used to represent HRQoL in the event-free health state	[redacted]	0.872	[redacted]	[redacted]
C3. C1, C2 & R3	[redacted]	**-0.053**	[redacted]	-
C4. B & C2	[redacted]	**0.340**	[redacted]	[redacted]

EAG=External Assessment Group; EFS=event-free survival; HR=hazard ratio; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table C Deterministic pairwise results (periadjuvant pembrolizumab versus surgery alone), PAS price for pembrolizumab and list prices for all other treatments

Scenario/EAG revisions	Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs		
A. Company clarification base case	[redacted]	**2.662**	[redacted]	-
R1) HR of one applied to pembrolizumab EFS curve after 62 months	[redacted]	2.580	[redacted]	[redacted]
R2) Time-constant EFS HR (fixed-effects model)	[redacted]	2.431	[redacted]	[redacted]
R3) Risk factor applied to general population mortality rates for patients assumed to be cured after 5 years	[redacted]	2.417	[redacted]	[redacted]
B. EAG preferred scenario (R1, R3)	[redacted]	**2.143**	[redacted]	[redacted]
C. EAG exploratory scenarios				
C1. Age- and sex-matched general population utility value used to represent HRQoL in the event-free health state	[redacted]	**2.551**	[redacted]	[redacted]
C2. B & C1	[redacted]	**2.039**	[redacted]	[redacted]

EAG=External Assessment Group; EFS=event-free survival; HR=hazard ratio; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table D Company clarification base case probabilistic results (fully incremental analysis), PAS price for pembrolizumab and list prices for all other treatments

Treatment	Cost	QALYs	ICER (£/QALY)
Surgery alone	[redacted]	[redacted]	-
Neoadjuvant nivolumab with chemotherapy	[redacted]	[redacted]	[redacted]
Periadjuvant pembrolizumab	[redacted]	[redacted]	[redacted]
Neoadjuvant chemotherapy	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table E EAG preferred scenario probabilistic results (fully incremental analysis), PAS price for pembrolizumab and list prices for all other treatments

Treatment	Cost	QALYs	ICER (£/QALY)
Neoadjuvant nivolumab with chemotherapy	[redacted]	[redacted]	-
Periadjuvant pembrolizumab	[redacted]	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]
Neoadjuvant chemotherapy	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

For further details of the revisions and exploratory analyses carried out by the EAG, see Section 6.8.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This appraisal focuses on pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small cell lung cancer (NSCLC). Within this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's document B, which is the company's full evidence submission. Additional evidence was provided by the company during the clarification stage.

2.2 Background

2.2.1 Disease

Lung cancer is the third most common cancer in the UK and accounts for 13% of all new cancer cases.[1] In 2022, approximately 39,000 patients in England and Wales were diagnosed with lung cancer.[2] The majority (90%) of lung cancer cases are NSCLC;[3] the two histological subtypes of NSCLC are squamous (25% to 30%) and non-squamous disease (75%).[4] Disease stage is determined using the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) Tumour–Node–Metastasis (TNM) system. The 8th edition[5,6] of the AJCC/UICC staging system was published in 2017 and is summarised in the CS (CS, Table 3). In England and Wales, around 30% of lung cancers are diagnosed at Stage I or Stage II.[3]

The population that is the focus of this appraisal is patients with Stage II to Stage IIIB (T3-4N2) resectable disease. Treatment options for patients with Stage II to Stage IIIB (T3-4N2) resectable disease are surgery, chemotherapy or chemoradiotherapy. Treatment is intended to be curative; however, the 5-year disease recurrence rates are 45% for patients with Stage IB, 62% with Stage II and 76% with Stage III[7] disease. Survival is poor, with approximately 62.7%, 40.9% and 16% of patients with Stage I, Stage II and Stage III disease, respectively, surviving for 5 years after diagnosis.[8]

2.2.2 Intervention

The mechanism and action of pembrolizumab are described in the CS (CS, Table 2). Pembrolizumab is a monoclonal antibody that binds to the programmed death-1 (PD-1) receptor thereby potentiating an immune response to tumour cells. The recommended dose of pembrolizumab is either 200mg every 3 weeks (Q3W) or 400mg every 6 weeks (Q6W); it is administered as an intravenous infusion (IV) over 30 minutes and is available in 100mg vials.

The Medicines and Healthcare products Regulatory Agency (MHRA) issued a marketing authorisation for pembrolizumab.[9] in May 2024. The licensed indication is in combination with platinum-containing chemotherapy as neoadjuvant treatment, then continued as a monotherapy as adjuvant treatment, for the treatment of resectable NSCLC at high risk of recurrence in adults.

The Summary of Product Characteristics (SmPC[9]) for pembrolizumab defines NSCLC at high risk of recurrence as: Stage II-IIIB (N2) according to the AJCC 8th edition[5] staging system: tumour size >4cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that invade thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve a mainstem bronchus with tumour >4 cm; or tumours >4 cm that cause obstructive atelectasis that extends to the hilum; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary lung cancer.

The treatment regimen[9] in the neoadjuvant setting is either, four cycles of pembrolizumab (200mg) Q3W or two cycles of pembrolizumab (400mg) Q6W given in combination with cisplatin plus gemcitabine or pemetrexed. Treatment should be discontinued in the event of disease progression that precludes definitive surgery or unacceptable toxicity. In the adjuvant setting, treatment with pembrolizumab monotherapy is 13 doses Q3W (200mg) or seven doses Q6W (400mg). Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity in the neoadjuvant setting should not receive pembrolizumab as an adjuvant treatment.

2.3 Company's overview of current service provision

Clinical guidelines

As discussed in the CS, NICE Guideline NG122[10] provides recommendations for the diagnosis and treatment of lung cancer. In summary, for resectable NSCLC, NG122[10] guidelines recommend surgery, radiotherapy, chemotherapy, alone or in combination, as follows:

- treatment with curative intent is surgical resection (lobectomy)
- adjuvant chemotherapy (cisplatin-based) is an option for patients who are fit enough (World Health Organisation [WHO] performance status of 0 or 1) and whose tumours were categorised at diagnosis as T1a–4, N1–2, M0 and T2b–4, N0, M0 with tumours greater than 4 cm in diameter.

- chemoradiotherapy prior to surgery is a treatment option for patients with locally advanced resectable tumours (Stage IIIA [N2]) who are fit enough to undergo the procedures.
- radical radiotherapy without surgery can be given with curative intent as a treatment option for patients with Stage I-IIA disease who decline or are contraindicated to lobectomy
- chemoradiotherapy is an option for patients with Stage II or Stage III disease who are unsuitable for, or who decline surgery

The company highlights (CS, p27) that the NG122[10] guideline recommends against the use of neoadjuvant chemotherapy for Stage I and Stage II disease. However, subsequent to the last NG122[10] update, NICE has recommended nivolumab with chemotherapy[11] as a treatment option in the neoadjuvant setting for patients with resectable disease of at least 4cm or node positive in adults (Stage IIA to Stage IIIB [N2]).

The company's overview of the treatment pathway and the proposed position of periadjuvant pembrolizumab is presented in Figure 1. Clinical advice to the EAG is that this pathway reflects the pathway for patients with resectable Stage II to IIIB (N2) NSCLC and the positioning of periadjuvant pembrolizumab. The company highlights (CS, p30) that there are currently no recommended periadjuvant immunotherapy treatments for resectable NSCLC.

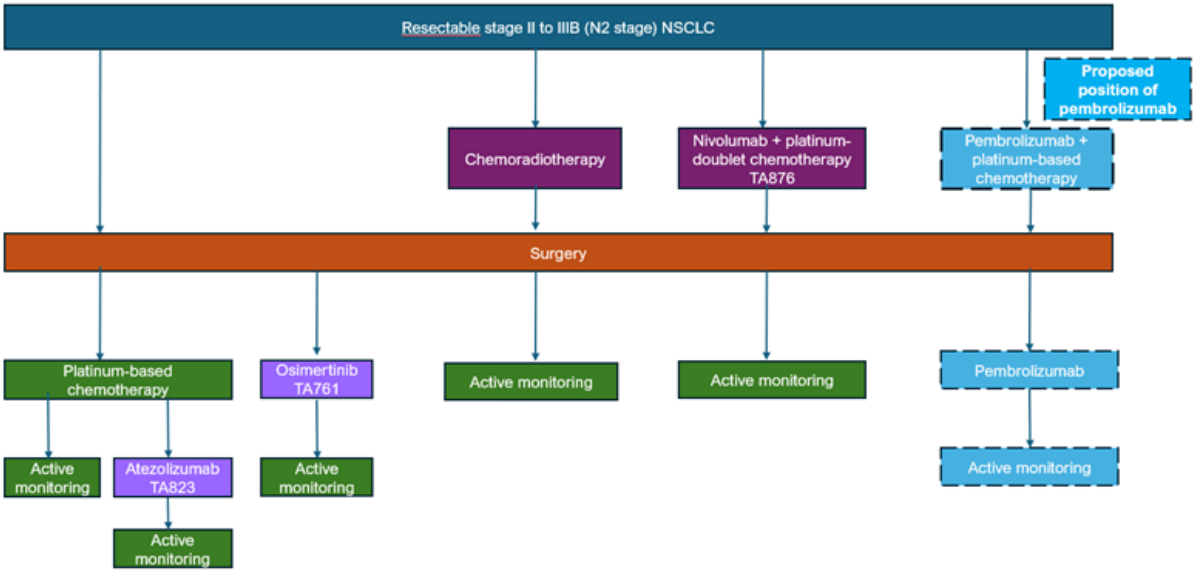

Figure 1 Company's proposed positioning of pembrolizumab

Atezolizumab and osimertinib are available through the Cancer Drugs Fund. Osimertinib is recommended for adjuvant use after complete resection in those who carry the epidermal growth factor receptor (EGFR) mutation[7] Atezolizumab is recommended for adjuvant use in those with programmed death-ligand 1 tumour proportion score (PD-L1 TPS) ≥50%[12]
Source: CS, Figure 2

Targetable mutations

The company states (CS, p26) that targetable mutations (e.g., epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]) are considered in the adjuvant setting and for patients with locally advanced or metastatic disease. The company notes that testing for biomarkers is a dynamic landscape and clinical advice to the EAG is that testing for biomarkers is routine in the neoadjuvant setting.

The use of periadjuvant treatment in the NHS

The company (CS, p29) explains that systemic treatments are administered in the neoadjuvant setting to inhibit the growth of circulating micro-metastases. Immunotherapy treatments boost the immune system to target circulating micro-metastases and any tumour cells that might be released during surgery. The purpose of adjuvant systemic treatment is to eradicate any remaining distant micro-metastases. The term periadjuvant treatment refers to the delivery of systemic treatment prior to and post-surgery.

There are no head to head trials that compare neoadjuvant chemotherapy versus periadjuvant chemotherapy (CS, p30) and no criteria to guide clinicians as to which patients would be suitable for neoadjuvant immunotherapy alone versus periadjuvant immunotherapy treatment (CS, p30). In the European Public Assessment Report (EPAR) for pembrolizumab,[13] the European Medicines Agency concludes that the design of the KEYNOTE-671 trial means that periadjuvant treatment can only be assessed as an overall strategy, i.e., it is not possible to compare the benefits of neoadjuvant and adjuvant phases of treatment.

Clinical advice to the company (CS, p30) is that '…the extent of the additional clinical benefit of periadjuvant treatment is currently uncertain and that [clinicians] would aim to avoid overtreating patients who may receive limited extra benefit of adjuvant treatment'. The company suggests (CS, p30) that a post-surgery histopathology assessment might be used to guide decisions about further treatment. Patients who do not achieve a complete pathological response (pCR), i.e., when there is evidence of residual viable tumour, could be considered for adjuvant treatment with an immunotherapy, whereas patients who achieve a pCR would be considered unlikely to benefit from continued immunotherapy. The company reports (CS, p30) the conclusions of a systematic review[14] that pCR after neoadjuvant chemotherapy with or without radiotherapy is associated with significant improvements in survival outcomes. Clinical advice to the company is that patients who achieve a pCR after surgery would likely not continue treatment.

2.4 Critique of company's definition of decision problem

A summary of the final scope[15] issued by NICE, the decision problem addressed by the company, and EAG comments are presented in Table 1 and further detail is provided in the text following this table (Section 2.4.1 to Section 2.4.8).

Table 1 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Intervention	Pembrolizumab with chemotherapy for neo-adjuvant treatment then pembrolizumab monotherapy as adjuvant treatment	As per final scope.	As per final scope.
Population	People with untreated resectable NSCLC	As per final scope.	As per final scope.
Comparator(s)	Established clinical management without pembrolizumab, which may include: • Neoadjuvant nivolumab with chemotherapy • Neoadjuvant chemoradiotherapy • Platinum based chemotherapy • Active monitoring • Durvalumab (subject to NICE appraisal) • Osimertinib (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)	**Addressed in the CS** • Neoadjuvant nivolumab with chemotherapy • Platinum-based chemotherapy • Active monitoring (i.e., surgery alone) **Not addressed in the CS** Neoadjuvant chemoradiotherapy MSD do not consider neoadjuvant chemoradiotherapy to be a relevant comparator for periadjuvant pembrolizumab. The recommendation in NG122 for use of neoadjuvant chemoradiotherapy plus surgery has only a weak "consider" type recommendation and the guidance is restricted to patients who are Stage IIIA-N2 and only those who are considered fit enough for surgery. Subgroup analyses for the specific population were not carried out because: • data were not reported separately in the comparator trials of interest for stage IIIA-N2 patients, therefore subgroup analysis was not feasible;	<u>Direct evidence</u> The company has presented clinical effectiveness evidence from the KEYNOTE-671 trial (neoadjuvant pembrolizumab with chemotherapy and adjuvant pembrolizumab versus neoadjuvant placebo with chemotherapy and adjuvant placebo). The EAG considers that the KEYNOTE-671 trial comparator arm represents neoadjuvant chemotherapy. <u>Indirect evidence</u> In the absence of direct evidence, the company has conducted EFS NMAs to compare periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy and versus neoadjuvant chemotherapy and versus active monitoring (surgery alone). In NG122,[10] chemoradiotherapy is only recommended for patients with operable Stage III (N2)

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
		• clinical experts consulted by the company confirmed that this regimen was either not in use or had been supplanted by neoadjuvant nivolumab plus chemotherapy. The treatments listed below are not considered relevant comparators as they are either under assessment by NICE or only available through the Cancer Drugs Fund, and are therefore not considered standard of care: • durvalumab;[16] • osimertinib;[7] • atezolizumab.[12]	disease. Clinical advice to the company and to the EAG is that, for this group of patients, chemoradiotherapy has been displaced by neoadjuvant nivolumab with chemotherapy NICE and the company agree that atezolizumab is not a relevant comparator. Discussions between the NICE and the company are ongoing re the inclusion of periadjuvant durvalumab and osimertinib as comparators in this appraisal. See Section 2.4.5 for details.
Outcomes	• Disease-free survival • Event-free survival • Pathological complete response • Overall survival • Response rates • Adverse effects of treatment • Health-related quality of life	Response rates were not collected in the KEYNOTE-671 study. Response rate might not be a clinically relevant outcome in the early Stage setting for lung cancer where systemic treatments are given to preclude development and growth of micro-metastases, with surgery the mainstay of the treatment plan. The KEYNOTE-671 trial assessed EFS, rather than DFS, as a co-primary outcome, which was defined as the time from randomisation to the first of: disease or local progression; inability to resect tumour; local or distant recurrence; or death. As noted in TA876,[11] in the neoadjuvant and periadjuvant setting, EFS is an appropriate outcome as it also captures events that preclude surgery.	<u>Direct evidence</u> The company has presented clinical effectiveness evidence from the KEYNOTE-671 trial for most of the outcomes listed in the final scope issued by NICE. The EAG accepts the company's rationale for not addressing the outcomes of DFS and response rates. <u>Indirect evidence</u> The company's NMAs provide clinical effectiveness for the outcome of EFS only. See Section 2.4.6 for details.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	The company did not include this row in CS, Table 1.	As per final scope.
Subgroups	If the evidence allows subgroups will be considered based on: • Whether pembrolizumab is used before and after surgery • PD-L1 tumour proportion score • Disease stage • Presence of biological or genetic markers	Presence of biological or genetic markers (other than PD-L1 status) was not routinely captured at patient enrolment in KEYNOTE-671. At the time of writing, presence of genetic markers, such as EGFR mutations and ALK translocations, is not routinely assessed at the point of neoadjuvant (and therefore periadjuvant) treatment for NSCLC in UK clinical practice. However, given the availability of treatments targeting EGFR and ALK abnormalities, testing is likely to become more common. Genetic markers are more commonly used to direct treatment for patients receiving adjuvant therapy, or for those with metastatic disease.	<u>Direct evidence</u> Analyses of EFS and OS from the KEYNOTE-671 trial are presented for the following subgroups: PD-L1 tumour proportion score, disease stage, EGFR mutation status and ALK translocation status. Subgroup analyses investigating the use of pembrolizumab before or after surgery are not available as the KEYNOTE-671 protocol mandated that all patients who underwent surgery continued to receive adjuvant pembrolizumab. The company conducted an

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
		Data on extent of use of pembrolizumab before and after surgery are reported in the submission. However, estimates of comparative clinical effectiveness by whether pembrolizumab was or was not used after surgery are not reported. The trial protocol for KEYNOTE-671 mandated that everyone who underwent surgery be given adjuvant treatment, irrespective of any patient characteristic. The cost effectiveness of actively selecting not to use pembrolizumab after surgery is explored in scenario analyses whereby it is assumed that patients who achieve a pCR after neoadjuvant therapy receive no further treatment after surgery. MSD note that KEYNOTE-671 was not powered to detect a difference in clinical effectiveness between the treatment groups in any subgroup. Thus, the results of subgroup analyses will be hypothesis generating and should be interpreted with caution.	exploratory scenario analysis (CS Table 73, scenarios 24-26) that removed the cost of adjuvant pembrolizumab for patients achieving a pCR.

ALK=anaplastic lymphoma kinase; CS=company submission; DFS=disease-free survival; EAG=External Assessment Group; EFS=event-free survival; EGFR=epidermal growth factor receptor; MSD=Merck, Sharpe, Dome; NSCLC=non-small cell lung cancer; pCR=pathological complete response; NMA=network meta-analysis; OS=overall survival; PD-L1=programmed death-ligand 1
Source: CS, Table 1 and EAG comment

2.4.1 Source of direct clinical effectiveness data

The company's main source of clinical effectiveness evidence for this appraisal is the KEYNOTE-671 trial. [17] The KEYNOTE-671 trial is a phase III, international, placebo-controlled randomised controlled trial (RCT) designed to assess the efficacy and safety of pembrolizumab as a periadjuvant treatment for patients with resectable Stage II, IIIA or IIIB (T3/4N2) NSCLC. In this trial, patients are treated with pembrolizumab (or placebo) with platinum-based chemotherapy in the neoadjuvant setting Q3W for four cycles; chemotherapy regimens administered in the neoadjuvant setting were cisplatin plus gemcitabine (squamous disease) and cisplatin plus pemetrexed (non-squamous disease). Following surgery, patients are treated with pembrolizumab monotherapy (or placebo) in the adjuvant setting (Q3W for 13 cycles). In total, 397 patients were randomised to the pembrolizumab arm, and 400 patients were randomised to the placebo arm. The KEYNOTE-671 trial is ongoing, but no longer recruiting.

All patients in the pembrolizumab arm of the KEYNOTE-671 trial were expected to be treated with adjuvant pembrolizumab; however, not all patients started adjuvant pembrolizumab treatment. It is, therefore, not possible to use KEYNOTE-671 trial data to compare the benefits of neoadjuvant versus adjuvant pembrolizumab. Further, clinical advice to the company (CS, p30), and published literature,[18] is that patients who achieve a pCR may be less likely to benefit from continued immunotherapy. The company explored the impact on cost effectiveness results of not using pembrolizumab after surgery (scenarios 24, 25 and 26).

2.4.2 Population

The company states (CS, p100) that the population discussed in the CS is in line with the anticipated marketing authorisation for periadjuvant pembrolizumab, i.e., pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, then continued as a monotherapy as adjuvant treatment, for adults with resectable NSCLC that is at high risk of recurrence. The difference between the final scope issued by NICE and the anticipated marketing authorisation for periadjuvant pembrolizumab is the inclusion of the phrase 'high risk of recurrence'. In response to clarification question C1, the company provided a list of criteria used to define 'high risk of recurrence' (

Box 1). The EAG considers that the KEYNOTE-671 trial population is in line with the population described in the final scope issued by NICE.

Box 1 Company definition of high risk disease

- Tumour size ≥4 cm; or
- Tumours of any size that are either accompanied by N1 or N2 status; or
- Tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or
- Tumours that involve the main bronchus <2cm distal to the carina but without involvement of the carina; or
- Tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or
- Tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.

Source: company response to clarification question C1

Clinical advice to the EAG is that patients enrolled in the KEYNOTE-671 trial (mean age 63.1 years) are younger than NHS patients with NSCLC who would be eligible for periadjuvant treatment (highest rates of NSCLC are reported in the 75 to 79 age group for females and the 85 to 89 age group for males [CS, p44]). Clinical advice to the EAG is that older, less fit patients may not be suitable for periadjuvant treatment.

2.4.3 Intervention

The intervention is pembrolizumab, administered in the neoadjuvant setting with platinum doublet chemotherapy and, in the adjuvant setting, as monotherapy; referred to, in the remainder of this report, as periadjuvant pembrolizumab. The recommended dose of KEYTRUDA in adults is either 200mg Q3W or 400mg Q6W administered as an IV infusion over 30 minutes.[13] See Section 2.2.2 for details of the marketing authorisation for pembrolizumab.

2.4.4 Included comparators

The company has provided evidence for three of the comparators listed in the final scope issued by NICE, namely neoadjuvant nivolumab with chemotherapy, neoadjuvant platinum-based chemotherapy and active monitoring (i.e., surgery alone). In the absence of any direct evidence comparing pembrolizumab with these treatments, the company has carried out network meta-analyses (NMAs). The KEYNOTE-671 trial provided evidence for periadjuvant pembrolizumab versus neoadjuvant chemotherapy. Three RCTs[19-21] compared surgery alone versus neoadjuvant chemotherapy provided evidence for active monitoring (surgery) and neoadjuvant chemotherapy. One RCT[22] provided evidence for the comparison of neoadjuvant nivolumab with chemotherapy versus neoadjuvant chemotherapy. The company only carried out event-free survival (EFS) NMAs.

Neoadjuvant nivolumab with chemotherapy

Clinical advice to the EAG is that neoadjuvant nivolumab with chemotherapy is the most relevant comparator to periadjuvant pembrolizumab.

Platinum-based chemotherapy

The final scope issued by NICE includes platinum based chemotherapy as a comparator; the setting in which platinum-based chemotherapy is delivered is not stated. The company has presented results for the comparison of periadjuvant pembrolizumab versus neoadjuvant chemotherapy (KEYNOTE-671 trial data). Clinical advice to the EAG is that neoadjuvant chemotherapy is rarely used in the NHS. Therefore, the EAG has not presented results for the comparison of periadjuvant pembrolizumab versus neoadjuvant chemotherapy in the main body of this report; results are provided in Appendix 8.1 (Table 44 and Table 45).

The company has not provided results for the comparison of periadjuvant pembrolizumab versus adjuvant platinum based chemotherapy. The company considers that it is not appropriate to compare outcomes from studies evaluating adjuvant treatments with outcomes from studies including periadjuvant or neoadjuvant treatments as the populations differ. Studies of adjuvant treatments include patients who have undergone resection, whilst studies of periadjuvant and neoadjuvant treatments include patients deemed to have resectable disease (CS Appendices, Section D.1.2).

2.4.5 Excluded comparators

The company considered that neoadjuvant chemoradiotherapy, periadjuvant durvalumab, adjuvant osimertinib, and atezolizumab were not relevant comparators. The company considered that periadjuvant durvalumab, adjuvant osimertinib, and atezolizumab were not relevant comparators as they were either under assessment by NICE or only accessible via the Cancer Drugs Fund (CDF) (CS, p16). At clarification, NICE asked the company to provide cost effectiveness results for the comparison of periadjuvant pembrolizumab versus periadjuvant durvalumab and adjuvant osimertinib (clarification questions B7 and B8 respectively).

Neoadjuvant chemoradiotherapy

The company does not consider that neoadjuvant chemoradiotherapy is a relevant comparator to periadjuvant pembrolizumab. The company (correctly) notes that in NG122,[10] chemoradiotherapy only has a 'weak' recommendation and is only recommended as a treatment option for patients with Stage IIIA (N2) disease. Clinical advice to the company and the EAG is that, in NHS practice, chemoradiotherapy has largely been displaced by neoadjuvant nivolumab with chemotherapy.

Periadjuvant durvalumab

At the time of writing the CS, the NICE appraisal of periadjuvant durvalumab (ID6220[23]) was ongoing. The NICE team highlighted that the first NICE Appraisal Committee (AC) meeting for periadjuvant durvalumab was scheduled to be held 1 month before the NICE AC meeting for periadjuvant pembrolizumab (9th July 2024 and 7th August 2024, respectively) and that if, at the July meeting, periadjuvant durvalumab were recommended by NICE for routine NHS use, then it should be considered a relevant comparator at the August meeting.

The company fully outlined reasons for not providing comparative periadjuvant durvalumab evidence in the response to clarification question B7. Key arguments presented by the company for excluding durvalumab from this appraisal are as follows:

1. Given the timelines, it is unclear whether durvalumab final draft Technology Appraisal Guidance will be available prior to the pembrolizumab NICE AC meeting. Further, it is not possible for Technology Appraisal Guidance for durvalumab to be issued prior to the pembrolizumab NICE AC meeting.

2. It is likely that the NICE AC durvalumab decision will be based on more mature durvalumab data than are currently publicly available; the only data from the pivotal durvalumab trial (AEGEAN) that are in the public domain were made available in early 2023 (11.7 months of follow-up). Were durvalumab recommended by NICE, it is not clear how the clinical and economic evidence considered at the NICE AC meeting in July could be incorporated into the company model in time for the August 2024 NICE AC meeting.

The company also put forward two alternative approaches that could be used to include durvalumab in the NICE AC decision-making process should periadjuvant durvalumab be recommended by NICE as a routine treatment option and if final draft guidance were available by 7 August 2024.

Adjuvant osimertinib

Osimertinib is currently recommended for use within the CDF as an adjuvant treatment after complete tumour resection in adults with Stage IB to Stage IIIA NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations (TA761[7]). NICE highlighted that the NICE CDF exit AC meeting for osimertinib is scheduled for June 2024 and it is possible that osimertinib will be recommended for routine use (and therefore become standard of care) before the NICE AC meeting for periadjuvant pembrolizumab on 7th August 2024.

In response to clarification question B8, the company highlighted that adjuvant osimertinib is only recommended by NICE as a treatment option for patients with EGFR-positive tumours who have undergone complete resection (TA761[7]). The EAG highlights that only 14 patients in the KEYNOTE-671 trial periadjuvant pembrolizumab arm had tumours that tested positive for the EGFR mutation. In the CS (CS, Appendices, Section D.1.2), the company states that it is not appropriate to compare outcomes from studies evaluating adjuvant treatments with outcomes from studies including periadjuvant or neoadjuvant treatments as the populations differ (the former have undergone resection, whilst the later include patients deemed to have resectable disease).

Atezolizumab

NICE and the company agree that atezolizumab, which is only recommended by NICE (within the CDF) as an option for patients with tumour PD-L1 tumour proportion score (TPS) ≥50% following adjuvant platinum-based chemotherapy (TA823[12]), is not a relevant comparator.

2.4.6 Outcomes

The outcomes assessed in the KEYNOTE-671 trial are EFS, pCR, major pathological response (mPR), OS, adverse events (AEs) and health-related quality of life (HRQoL); disease-free survival (DFS) and response rate evidence were not collected.

Clinical advice to the EAG agrees with the company (CS, Table 1) that EFS (defined as time from randomisation to the first of: disease or local progression; inability to resect tumour; local or distant recurrence; or death) is an appropriate outcome in the periadjuvant setting.

Response rate was not an outcome in the KEYNOTE-671 trial. The company considers (CS, Table 1) that response rate might not be a clinically relevant outcome for patients treated in the neoadjuvant, adjuvant, or periadjuvant settings. Surgery is the key treatment and systemic treatments are given to prevent the development and growth of micro-metastases.

The only outcome assessed via the company's NMAs is EFS. KEYNOTE-671 trial OS data were immature, meaning that conclusions cannot be drawn about the relative effectiveness of periadjuvant pembrolizumab versus comparator treatments.

The company did not conduct AE, HRQoL or pCR NMAs. The EAG is satisfied with the company arguments for not conducting these NMAs (company response to clarification question A2). In the response, the company reported that feasibility assessment results showed that it would not be possible to conduct AEs or HRQoL NMAs due to limitations in the evidence base, namely, differences in outcome definitions and differences in the timepoint of

assessments. The company explained that pCR was reported in five trials (CheckMate-816,[22] CHEST,[21] Felip,[19] KEYNOTE-671,[17] and Pisters[20]), but was only available for the chemotherapy arm in the chemotherapy versus surgery trials (CHEST,[21] Felip,[19] Pisters[20]), so relative pCR could not be assessed in these studies. The company highlighted that although a pCR NMA is technically feasible, results would have a relatively small impact on decision making because pCR is a predictive surrogate outcome (similar to complete response and partial response in in trials of metastatic carcinomas).

2.4.7 Subgroups

As listed in the final scope issued by NICE, evidence is available from the KEYNOTE-671 trial for EFS and OS by PD-L1 tumour proportion score, disease stage, EGFR mutation status and ALK translocation status (CS, Figure 8 and CS, Figure 9). The company highlights (CS, Table 1) that the KEYNOTE-671 trial was not powered to detect a difference in clinical effectiveness between any subgroups and the results of the subgroup analyses presented in the CS should be interpreted with caution.

2.4.8 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 36.9 year time period (which the company considered was equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

Pembrolizumab and nivolumab are available to the NHS at confidential Patient Access Scheme (PAS) prices. The confidential price of nivolumab is not known to the company. Cost effectiveness results generated using the discounted prices for all drugs are presented in a confidential appendix.

The company does not consider that periadjuvant pembrolizumab qualifies for a severity modifier (CS, p161).

2.4.9 Equality considerations

The company did not raise any special considerations, including those relating to equity or equality.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company carried out a systematic literature review (SLR) to identify and select relevant evidence of the clinical effectiveness of pembrolizumab in combination with platinum-based chemotherapy before surgery (neoadjuvant), followed by pembrolizumab alone after surgery (adjuvant) versus platinum-based chemotherapy alone; full details of the SLR methods are presented in the CS (Appendix D). An assessment of the extent to which the SLR was conducted in accordance with the LR*i*G in-house systematic review checklist is presented in

Table 2. The EAG considers that the company's review was conducted to a good standard. The EAG conducted its own searches; these and did not identify any additional trials that provided information on the clinical effectiveness of periadjuvant (i.e., adjuvant and neoadjuvant) pembrolizumab.

Table 2 EAG appraisal of the company's systematic review methods

Review process	EAG	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D.1
Were appropriate sources searched?	Yes	CS, Appendix D.1.1
Was the timespan of the searches appropriate?	Yes	CS, Appendix D.1.1
Were appropriate search terms used?	Yes	CS, Appendix D.1.1, Table 1, Table 2, Table 3
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix D.1.2, Table 4
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D.1.2.1
Were data extracted by two or more reviewers independently?	Yes	CS, Appendix D.1.2.2
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	The quality of the RCTs included in the NMAs was assessed using the Cochrane Collaboration's Risk of Bias tool, version 2.[24] (CS, Appendix D.1.2.3)
Was the quality assessment conducted by two or more reviewers independently?	Yes	See response to clarification QC2
Were attempts to synthesise evidence appropriate?	Yes	Company NMAs compared the clinical effectiveness of periadjuvant pembrolizumab versus neoadjuvant nivolumab+chemotherapy, neoadjuvant chemotherapy, surgery alone. The EAG critique of the company's methods is presented in Section 3.7 of this report

CS=company submission; EAG=External Assessment Group; NMA=network meta-analysis; RCT=randomised controlled trial
Source: LR*i*G in-house checklist

3.2 EAG summary and critique of clinical effectiveness evidence

3.2.1 Trials included in the company's systematic literature review

The company SLR identified one relevant, international, double-blind, phase III RCT, the KEYNOTE-671 trial. The KEYNOTE-671 trial is an ongoing trial that provides clinical effectiveness evidence for the efficacy of pembrolizumab as a periadjuvant treatment for patients with resectable Stage II, IIIA or IIIB (T3/4N2) NSCLC.

To compare the clinical effectiveness of periadjuvant pembrolizumab versus three of the comparators listed in the final scope issued by NICE (namely, neoadjuvant nivolumab with chemotherapy, platinum based chemotherapy and surgery alone [as a proxy for active monitoring]), the company conducted NMAs. The EAG's summary and critique of the company's NMAs is presented in Section 3.7. Details of the comparator trials included in the company NMAs are available in the CS (CS, Appendix D, Section D.1.3).

3.2.2 Characteristics of the KEYNOTE-671 trial

A summary of the KEYNOTE-671 trial design is presented in the CS (Figure 5). The treatments administered in the trial are presented in Table 3.

Table 3 Treatments in the KEYNOTE-671 trial

Trial setting	Pembrolizumab[a] (n=397)	Placebo[b] (n=400)
Neo-adjuvant	Pembrolizumab (200mg)+platinum doublet chemotherapy Q3W (4 cycles)	Placebo+platinum doublet chemotherapy Q3W (4 cycles)
Adjuvant	Pembrolizumab (200mg) Q3W (13 cycles)	Placebo Q3W (13 cycles)

[a] Pembrolizumab refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab
[b] placebo refers to the same treatment plan with placebo substituted for pembrolizumab
Q3W=every 3 weeks

Pembrolizumab neoadjuvant treatment was administered Q3W for four cycles and pembrolizumab adjuvant treatment was administered Q3W for 13 cycles. The platinum doublet chemotherapy administered to patients with non-squamous disease was cisplatin (75mg/m^2) with pemetrexed (500mg/m^2). The platinum doublet chemotherapy administered to patients with squamous disease was cisplatin (75mg/m^2) with gemcitabine (100mg/m^2).The dose of pembrolizumab was 200mg. Placebo was administered as normal saline.

Randomisation was stratified by Stage (II or III), TPS <50% or ≥50%), histology (squamous or non-squamous) and region (East Asia or non-East Asia). Patients were recruited from 189 treatment centres in 25 countries in Europe, East Asia, North America, South America (CS, Table 8). Ten patients from five UK treatment centres were enrolled in the KEYNOTE-671 trial (CS, p40).

The final OS data analysis for the KEYNOTE-671 trial is scheduled for the time when approximately [redacted] patients have died, expected approximately 96 months after the first patient was randomised (CS, Table 12). The primary trial outcomes are investigator-assessed EFS and OS.

3.2.3 Demographic and disease characteristics of KEYNOTE-671 trial patients

The baseline KEYNOTE-671 trial patient demographic characteristics and patient disease characteristics are provided in the CS (Table 10). The EAG agrees with the company (CS, p43) that characteristics are balanced between the trial arms. Clinical advice to the EAG is that KEYNOTE-671 trial patients are younger (mean 63.1 years [CS, Table 10]) than NHS patients (average 70 years) and that patients with squamous disease are under-represented in the trial. The company has highlighted (CS, p44) that in the UK, highest rates of NSCLC are reported in the 75 to 79 age group for females and the 85 to 89 age group for males. The company considers (CS, p44) that it is usual for clinical trials to enrol a cohort that is younger than the average patient who would receive the treatment in clinical practice.

3.2.4 Quality assessment of the KEYNOTE-671 trial

The company conducted a quality assessment of the KEYNOTE-671 trial using the Cochrane Risk of Bias tool for RCTs (ROB-2).[24] The company has presented an assessment of the risk of bias for the outcome of EFS (CS, Table 13). The EAG agrees with the company's assessment (CS, Table 13) and agrees with the company's conclusion (CS, p50) that the trial is at low risk of bias.

3.2.5 Statistical approach used to analyse KEYNOTE-671 trial data

Information relevant to the statistical approach taken by the company to analyse KEYNOTE-671 trial data has been extracted from the CS and the Clinical Study Report[17] (CSR). The CSR includes the trial statistical analysis plan (TSAP), the supplementary statistical analysis plan (sSAP), the trial protocol. A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse data from the included trial is provided in Table 4.

Table 4 EAG assessment of statistical approach used to analyse KEYNOTE-671 trial data

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	Analyses of the co-primary endpoints of EFS and OS, and of the secondary outcomes of mPR and pCR, were based on the ITT population, defined as all randomised patients who were analysed in the treatment arm to which they were randomised (CS, p47) Analyses of patient reported outcome (PRO) endpoints were conducted using the PRO full analysis set (FAS) population, defined as all randomised participants who had at least 1 PRO assessment available and received at least 1 dose of study

Item	EAG assessment	Statistical approach with EAG comments
		intervention (CS, p47) Analyses of safety data were based on the 'all participants as treated' (APaT) population, which included randomized participants who received at least 1 dose of allocated study treatment (CS, p48) The EAG is satisfied that these populations were clearly defined and pre-specified in the TSAP (TSAP, p109).
Was an appropriate sample size calculation pre-specified?	Yes	The planned sample size is approximately 786 participants. The trial is event driven and completes after substantial efficacy evidence of EFS and/or OS are observed. Assumptions used to generate the sample size and power calculations are presented (CS, p48) At 416 EFS events, the study has 90% power for detecting a HR of 0.7 at a 1.0% (one-sided) significance level. At [redacted] deaths, the study has 90% power for detecting a HR of 0.7 at a 1.48% (one-sided) significance level. Based on the time that approximately 326 EFS events have been observed, the study has 99.1% power for detecting a 20 percent point difference in mPR rate and 99.3% power for detecting a 16 percent point difference in pCR rate at a 0.01% (one-sided) significance level. The EAG is satisfied that the sample size is appropriate and was pre-specified in the TSAP (TSAP, p111)
Were all protocol amendments made prior to analysis?	No	Amendment 11 was added on 29th November 2022, i.e. after IA1 and prior to IA2. Amendment 11 added extended annual imaging to the post-treatment follow-up phase and specified the assessments to be conducted during that time period (CSR p59). The EAG considers that this change is minor and is well-justified in the CSR (CSR, pp2478 to 2483)
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	Primary and secondary efficacy endpoints are defined in CS (CS, p41). Definitions and analysis approaches for these endpoints were pre-specified in the TSAP (TSAP, Table 10). The overall type I error rate over the multiple endpoints was controlled at 2.5% (one-sided) for all hypotheses using the graphical approach of Maurer and Bretz.[25] Initially, a 0.01% (one-sided) type I error rate was allocated to test mPR rate, 0.01% (one-sided) was allocated to test pCR rate,1.0% (one-sided) allocated to test EFS and 1.48% (one-sided) allocated to test OS. The graphical approach of Maurer and Bretz[25] was applied to re-allocate alpha among the hypotheses for mPR rate, pCR rate, EFS and OS. Group sequential methods were used to allocate alpha among the interim and final analyses for the EFS and OS endpoints. The multiplicity graph for type 1 error control is presented the CS (Figure 6) and the TSAP (Figure 2). The EAG considers that the multiplicity strategy was appropriate.
Was the analysis approach for PROs appropriate and pre-specified?	Yes	Mean change from baseline in the neoadjuvant phase and in the adjuvant phase in global health status/quality of life using the EORTC QoL questionnaire QLQ-C30 (items 29 and 30) was assessed as a secondary outcome (CS, p42). The analysis approach for this outcome is documented in the TSAP (Section 10.6.3). All other PROs were assessed as exploratory endpoints and were prespecified in the sSAP (sSAP, p23).
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Safety was specified as a secondary endpoint. The analysis of AEs followed a tiered approach that was pre-specified in the TSAP (Section 10.6.2).
Was a suitable approach employed for handling missing data?	Yes	The company's approach to missing data is described in the TSAP (Section 10.6).

Item	EAG assessment	Statistical approach with EAG comments
Were all subgroup and sensitivity analyses pre-specified?	Yes	The subgroup analyses are prespecified in the TSAP (Section 10.10).

AE=adverse event; APaT=all patients as treated; CS=company submission; CSR=clinical study report; EAG=External Assessment Group; EFS=event-free survival; EORTC=European Organisation for Research and Treatment of Cancer; FAS=full analysis set; mPR=major pathological response; OS=overall survival; pCR=pathological complete response; PRO=patient reported outcome; QoL=quality of life; sSAP=supplementary statistical analysis plan; TSAP=trial statistical analysis plan
Source: CS, CSR[17] (trial protocol, sSAP, TSAP are available in the CSR)

3.3 Efficacy results from the KEYNOTE-671 trial

The KEYNOTE-671 trial clinical efficacy results presented in the CS are from the pre-specified IA2 data cut (10th July 2023). Mean duration of follow-up was 32 months (standard deviation [SD]=15.2) in the pembrolizumab arm and 30 months (SD=14.2) in the placebo arm (CS, Table 14). The schedule for the analysis of KEYNOTE-671 trial key endpoints is presented in Table 5.

Table 5 KEYNOTE-671 trial: schedule for the analysis of key endpoints

Analysis	Key endpoints	Timing	Purpose
IA1	EFS OS mPR rate pCR rate	~326 EFS events have been observed and ~5 months after last participant was randomised	EFS interim analysis (~78% of target EFS events) OS interim analysis (~41% of target OS events) mPR and pCR rate analyses
IA2	EFS OS	[redacted] EFS events have been observed (~60 months after first participant was randomised)	EFS final analysis OS interim analysis ([redacted]% of target OS events)
IA3	OS	[redacted] deaths have been observed (~72 months after first participant was randomised)	OS interim analysis ([redacted]% of target OS events)
IA4	OS	[redacted] deaths have been observed (~84 months after first participant was randomised)	OS interim analysis ([redacted]% of target OS events)
FA	OS	[redacted] deaths have been observed (~96 months after first participant was randomised)	OS final analysis

EFS=event-free survival; FA=final analysis; IA=interim analysis; mPR=major pathological response; OS=overall survival; pCR= pathological complete response
Source: CS, Table 12

3.3.1 Disposition of patients in the KEYNOTE-671 trial at IA2

The disposition of patients at IA2 is presented in the CS (CS, Table 10). At this point, 69.5% of patients in the pembrolizumab arm and 61.8% of patient in the placebo arm were still being followed-up. Key patient disposition data is presented in Table 6. Throughout this section of the EAG report, the treatment regimens in all tables are abbreviated. 'Pembrolizumab' refers to neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant

pembrolizumab and 'placebo' refers to the same treatment plan with placebo substituted for pembrolizumab.

Table 6 KEYNOTE-671 trial: company summary of patient disposition data

	Pembrolizumab (N=397)	Placebo (N=400)
Proportion of patients not undergoing surgery	17.9%	20.5%
Proportion of patients completing study treatment at IA2	48.2%	43.6%
Most frequent reason for treatment discontinuation	AE: 21.7%	PD: 26.6%
Patients remaining on study treatment at IA2	0	0
Proportion of patients who discontinued from the trial	30.5%	38.3%
Most common reason for trial discontinuation	Death: 27.5%	Death: 35.3%
Patients being followed-up	69.5%	61.8%

AE=adverse event; PD=progressed disease; IA2=interim analysis 2
Source: CS, p52

3.3.2 Event-free survival at IA2 (co-primary outcome)

The EFS analysis, based on investigator assessment at IA2, is presented in Table 7; this analysis is the final EFS analysis (Table 5). Median EFS was statistically significantly longer in the pembrolizumab arm at 47.2 months (95% confidence interval [CI]: 32.9 to NR) compared with the placebo arm at 18.3 months (95% CI: 14.8 to 22.1). The most common first EFS event in the pembrolizumab and placebo arms was disease progression or recurrence (29.7% and 46.8%, respectively).

Table 7 KEYNOTE-671 trial: event-free survival (ITT population)

Outcome	Pembrolizumab (N=397)	Placebo (N=400)
Number of events, n (%)	174 (43.8)	248 (62.0)
Median EFS, months (95% CI, months)[a]	47.2 (32.9 to NR)	18.3 (14.8 to 22.1)
EFS HR (95% CI)[b]	0.59 (0.48 to 0.72), p<0.00001	
Type of first event in EFS analysis n (%)		
No event	223 (56.2)	152 (38.0)
Event	174 (43.8)	248 (62.0)
Progression/recurrence	118 (29.7)	187 (46.8)
Local progression preventing surgery	1 (0.3)	6 (1.5)
Inability to resect the tumour	5 (1.3)	15 (3.8)
Death	50 (12.6)	40 (10.0)

[a] From product-limit (Kaplan–Meier) method for censored data
[b] Based on Cox regression model with treatment as a covariate stratified by Stage (II vs III), TPS (≥50% vs <50%), histology (squamous vs non-squamous) and region (East-Asia vs non-East Asia), where region is collapsed for Stage II TPS ≥50% non-squamous and Stage II TPS ≥50% squamous
CI=confidence interval; EFS=event-free survival; HR=hazard ratio; ITT=intention to treat; NR=not reached
Source: adapted from CS, Table 16

The company highlights (CS, p54) that:

- the Kaplan-Meier (K-M) plot (CS, Figure 7) shows that the pembrolizumab arm separates from the placebo arm at 5 months and remains separated thereafter
- the forest plot (CS, Figure 8) shows that the benefit of pembrolizumab versus placebo was evidenced across all pre-specified subgroups.

3.3.3 Overall survival at IA2 (co-primary outcome)

Overall survival results at IA2 from the KEYNOTE-671 trial are presented in Table 8. The IA2 analysis is an interim analysis of OS. The final OS analysis is planned to take place when approximately [redacted] deaths have occurred, approximately 8 years after the first patient was randomised to the trial (Table 5). At IA2, median OS in the pembrolizumab arm had not been reached and median OS in the placebo arm was 52.4 months (95% CI: 45.7 to not reached [NR]).

Table 8 KEYNOTE-671 trial: overall survival at IA2 (ITT population)

Outcome	Pembrolizumab (N=397)	Placebo (N=400)
Number of events, n (%)	110 (27.7)	144 (36.0)
Median OS, months (95% CI, months)[a]	NR (NR to NR)	52.4 (45.7 to NR)
OS HR (95% CI)[b]	0.72 (0.56 to 0.93), p=0.00517	

[a] From product-limit (Kaplan–Meier) method for censored data
[b] Based on Cox regression model with treatment as a covariate stratified by Stage (II vs III), TPS (>=50% vs <50%), Histology (squamous vs non-squamous) and Region (East-Asia vs. non-East Asia), where Region and Histology are collapsed for Stage II TPS >=50%; Region is collapsed for Stage III TPS >=50% squamous and Stage II TPS <50% non-squamous
CI=confidence interval; HR=hazard ratio; IA2=interim analysis 2; ITT=intention to treat; NR=not reached; OS=overall survival
Source: adapted from CS, Table 17

The company highlights (CS, p56) that:

- the K-M plot (CS, Figure 9) shows that the pembrolizumab arm separates from the placebo arm at 16 months and remains separated thereafter
- the forest plot (CS, Figure 10) shows that the benefit of pembrolizumab versus placebo was generally evidenced across all prespecified subgroups, although the estimated HR for some analyses is close to 1 and the HR for the East Asia subgroup is above 1. However, the OS data are immature, the number of events in some subgroups is small and the CIs are wide

3.3.4 Secondary outcomes

The main analysis of the secondary outcomes of pCR and mPR rates was conducted at IA1; statistically significant results were reported (CS, p59 and p60). The company highlights (CS, p59 and p60) that the IA2 results reported in the CS are descriptive only.

The KEYNOTE-671 trial pCR and mPR rates are presented in

Table 9 and Table 10, respectively. A pCR was recorded in 18.1% of patients in the pembrolizumab arm and 4.0% of patients in the placebo arm. The difference in response rates was statistically significant. The company reports (CS, p59) that differences in pCR rates were identified across all pre-specified subgroups and were consistent with ITT population results.

A mPR was recorded for 30.2% of patients in the pembrolizumab arm versus 11% of patients in the placebo arm. The difference in mPR rates was statistically significant.

Table 9 KEYNOTE-671 trial: pathological complete response rate (ITT population)

Treatment	N	Number of patients achieving pCR	pCR rate (%) (95% CI)	Difference (%)	
				Estimate (95% CI)[a]	p-value[b]
Pembrolizumab	397	72	18.1 (14.5 to 22.3)	14.2 (10.1 to 18.7)	<0.00001
Placebo	400	16	4.0 (2.3 to 6.4)		

[a] Based on Miettinen & Nurminen[26] method stratified by Stage (II vs III), TPS (>=50% vs <50%), histology (squamous vs non-squamous) and region (East-Asia vs non-East Asia)
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % >0
CI=confidence interval; pCR=pathological complete response
Source: CS, Table 18

Table 10 KEYNOTE-671 trial: major pathological response (ITT population)

Treatment	N	Number of patients achieving mPR	mPR Rate (%) (95% CI)	Difference	
				Estimate (95% CI)[a]	p-value[b]
Pembrolizumab	397	120	30.2 (25.7 to 35.0)	19.2 (13.9 to 24.7)	<0.00001
Placebo	400	44	11.0 (8.1 to 14.5)		

[a] Based on Miettinen and Nurminen[26] method stratified by Stage (II vs III), TPS (≥50% vs <50%), histology (squamous vs non-squamous) and region (East-Asia vs non-East Asia)
[b] One-sided p-value for testing. H_0: difference in %=0 versus H1: difference in % >0.
CI=confidence interval; mPR=major pathological response
Source: CS, Table 19

3.4 Health-related quality of life

Health-related quality of life data were collected from the PRO FAS population using the EORTC QLQ-C30[27] and the EQ-5D-5L visual analogue scale (VAS)[28] tools. The PRO FAS population includes all randomised participants who had had at least one PRO assessment and had received at least one dose of study intervention (pembrolizumab arm: n=389; placebo arm: n=392).

Baseline assessments were carried out at neoadjuvant cycle 1 and mean change from baseline scores were calculated at neoadjuvant Week 11. At the database cut-off date (10th July 2023, IA2), the company calculated mean change from baseline using data collected at Week 10 of the adjuvant phase. Week 10 was chosen to ensure that questionnaire completion rates were approximately ≥60% and compliance rates were approximately ≥80% across treatment arms (CS, p61).

3.4.1 EORTC QLQ-C30 questionnaire results (Full analysis set)

EORTC QLQ-C30[27] questionnaire data results for item 29 (global health status) and item 30 (quality of life) are summarised narratively in the main body of the CS (CS, p61) and are presented graphically in an Appendix (CS, Appendix E3, Figure 13). The company highlights (CS, p61) that:

- at baseline, the completion rate of the questionnaire was >90% and was the same in both arms (98.2%)
- completion rates at both Week 11 of the neoadjuvant phase for the pembrolizumab arm and the placebo arm were 87.1% and 88.9%, respectively and rates at Week 10 of the adjuvant phase were 68.6% and 62.1%, respectively
- global health status/quality of life scores decreased relative to baseline in both treatment arms in the neoadjuvant phase, showing deterioration in QoL; however, in the adjuvant phase, scores were stable relative to baseline
- there was no statistically significant difference between treatment arms in change from baseline score in either the neoadjuvant or adjuvant phase. In the neoadjuvant phase, the difference in least squares (LS) means was 1.43 (95% CI: –1.64 to 4.49; p=0.3611). In the adjuvant phase the difference in LS means was 2.22 (95% CI: –0.58 to 5.02; p=0.1197).

3.4.2 EQ-5D-5L VAS results (FAS population)

EQ-5D-5L VAS assessment results are presented in the CS (CS, Table 20). The company highlights (CS, p61) that:

- at baseline, the completion rate of the EQ-5D-5L VAS tool was >90% and rates were similar in the pembrolizumab and placebo arms (98.5% and 98.2%)
- completion rates at Week 11 in the neoadjuvant phase for the pembrolizumab arm and the placebo arm were 87.3% and 89.2%, respectively and at Week 10 in the adjuvant phase, rates were 68.6% and 61.9%, respectively
- in the neoadjuvant phase, at Week 11, EQ-5D-5L VAS scores [redacted] relative to baseline in both treatment arms, indicating a [redacted] of QoL. There was [redacted] between the pembrolizumab and placebo arms in change in EQ-5D-5L VAS (LS means difference=[redacted])
- in the adjuvant phase, at Week 10, EQ-5D-5L VAS results were [redacted] in both the pembrolizumab and placebo arms. There was [redacted] in score between the pembrolizumab and placebo arms (LS means difference=[redacted].

3.5 EAG conclusions: HRQoL

The EAG considers that HRQoL trends in the neoadjuvant phase (reduced QoL) and adjuvant phase (stable scores) were similar for patients in the pembrolizumab and placebo arms; HRQoL scores did not differ significantly between the trial arms.

3.6 Safety and tolerability results from the KEYNOTE-671 trial

KEYNOTE-671 trial safety data are reported for the 'all patients as treated' (APaT) population (pembrolizumab arm: n=396; placebo arm: n=399). The recorded AEs are events that were experienced by patients across the duration of the trial (i.e., neoadjuvant and adjuvant phases).

3.6.1 Treatment exposure in the KEYNOTE-671 trial

The median duration of treatment exposure is reported in the CS (CS, Table 28 and Table 29). The company highlights that:

- patients in the pembrolizumab arm were treated for longer than patients in the placebo arm ([redacted])
- more patients in the pembrolizumab arm completed ≥12 months of treatment ([redacted]) than patients in the placebo arm ([redacted]).

3.6.2 Summary of adverse events from the KEYNOTE-671 trial

A summary of KEYNOTE-671 trial AEs is presented in Table 11. The EAG agrees with the company that the trial AEs rates are similar in the pembrolizumab and placebo arms (99.5% versus 98.7%). The EAG highlights that treatment discontinuation rates due to AEs were higher in the pembrolizumab arm than in the placebo arm (25.8% versus 17.5%).

Table 11 KEYNOTE-671 trial: adverse event summary

	Pembrolizumab (n=396)		Placebo (n=399)	
	n	%	n	%
One or more adverse events	394	99.5	394	98.7
No adverse event	2	0.5	5	1.3
Drug-related adverse events	383	96.7	381	95.5
Grade 3-5 adverse events	257	64.9	213	53.4
Grade 3-5 drug-related adverse events	179	45.2	151	37.8
Serious adverse events	165	41.7	133	33.3
Serious drug-related adverse events	73	18.4	58	14.5
Death	26	6.6	15	3.8
Death due to a drug-related adverse event	4	1.0	3	0.8
Discontinued any drug due to an adverse event	102	25.8	70	17.5

Source: Extracted from CS, Table 30

3.6.3 Most frequently reported KEYNOTE-671 trial adverse events

The AEs reported in either treatment arm of the KEYNOTE-671 trial (incidence of ≥10%) are presented in the CS (CS, Table 31). The company highlights (CS, p67) that the AEs more frequently reported in the pembrolizumab arm than the placebo arm were hypothyroidism (10.9% versus 1.5%), rash (17.4% versus 8.5%), fatigue (31.6% versus 25.3%), insomnia (12.9% versus 6.5%), dyspnoea (18.4% versus 13.0%), alanine aminotransferase increase

(14.9% versus 10.3%), pruritus (13.4% versus 8.8%), pyrexia (12.6% versus 8.0%), and peripheral oedema (10.1% versus 6.0%).

3.6.4 KEYNOTE-671 trial drug-related adverse events

The drug-related AEs, reported in either treatment arm of the KEYNOTE-671 trial, with an incidence of ≥5% are presented in the CS (CS, Table 32). The company highlights (CS, p88) that rates of drug-related AEs were similar in the pembrolizumab arm and in the placebo arm (96.7% versus 95.5%) and that AE rates with an incidence of ≥30% (nausea, decrease in neutrophil count and anaemia) were also similar across the treatment arms.

3.6.5 Categories of KEYNOTE-671 trial adverse events

Rates of specific AE categories arising during the KEYNOTE-671 trial are presented in the CS (CS, pp89-94). The rates and types of AEs observed appear to be consistent with the AEs typically associated with the use of pembrolizumab and platinum based chemotherapy.

3.6.6 EAG conclusions: safety and tolerability

Clinical advice to the EAG is that the company's safety and tolerability data raise no specific or unusual concerns or signals for the KEYNOTE-671 trial population. However, clinical advice to the EAG cautions that patients treated in the NHS are generally older than the patients in the KEYNOTE-671 trial and, consequently, may be less tolerant of immunotherapy treatment.

3.7 Summary and critique of the NMAs

The company considered that neoadjuvant nivolumab with chemotherapy, neoadjuvant platinum-based chemotherapy and active monitoring (i.e., surgery alone) were the relevant comparators to periadjuvant pembrolizumab (Section 2.4.4 of this EAG report). The company's SLR did not identify any head-to-head trials investigating the efficacy of periadjuvant pembrolizumab versus any of the relevant comparators and therefore the company conducted NMAs.

3.7.1 Identification of trials for inclusion in the NMAs

In terms of interventions and comparators, the company SLR eligibility criteria were broader than the requirements of the final scope issued by NICE and, although the company's SLR identified 32 RCTs, the company considered that only five[17,19-22] of these RCTs were relevant; these five[17,19-22] RCTs were included in the company NMAs.

3.7.2 Characteristics of trials included in the NMAs

Key characteristics (patients and trial designs) of the RCTs included in the NMAs are provided in the CS (CS, Table 21 and Appendix D). A summary of the five included RCTs[17,19-22] (participants and designs) is presented in Table 12.

As described in the CS (CS, pp64-65), results from the three trials[19-21] that included surgery alone were published over 10 years ago. Further, two trials[20,21] were terminated early following the publication of results that showed benefits for adjuvant chemotherapy over surgery alone. In addition, the staging systems used in three of the trials[17,21,22] vary, and the staging systems used in the other two trials (Felip 2010[19] and Pisters 2010[20]) were not reported. The risk of bias assessments reflect the methodological limitations linked to the early termination of trials and the lack of detail available in the trial publications, in particular, randomisation methods and the extent of blinding.

The EAG notes that median follow-up differed across the trials, ranging from 29.5 months[22] to 64 months.[20] Additionally, there are differences in the patient inclusion criteria and the proportion of patients diagnosed at each disease stage.

Clinical advice to the EAG is that current standard of care for NHS patients with non-squamous NSCLC is platinum doublet pemetrexed, as given to patients in the CheckMate-816[22] and KEYNOTE-671[17] trials. Patients with non-squamous disease enrolled in the three chemotherapy versus surgery RCTs[19-21] received either platinum doublet gemcitabine[21] or platinum doublet paclitaxel[19,20]).

Table 12 Summary details of RCTs included in the company's NMAs

	CHEST[21] (n=270)	Felip 2010[19] (n=624)	Pisters 2010[20] (n=354)	CheckMate-816[22] (n=358)	KEYNOTE-671[17] (N=797)
Population	NSCLC Stages I (except for T1N0), II, or IIIA (T3N1; excluding superior sulcus)	NSCLC Stages IA with tumour size >2cm, IB, II, or T3N1	NSCLC Stages IA–IIIB	NSCLC Stage IB (≥4 cm) to IIIA	NSCLC Stage II or IIIA/B (T3-4N2)
Staging criteria	AJCC v5[29]	Not reported	Not reported	AJCC v7[30]	AJCC v8[5]
Disease stage	IB/IIA: 52%, IIB/IIIA: 48%	Unclear[a]	IB/IIA: 68%, IIB/IIIA: 32%	IB or II: 35.4% IIIA: 64.6%	II: 30%, IIIA: 55%, IIIB: 14%
Non-squamous disease	36%	48%	36%	49%	57%
Intervention	Neoadjuvant CTX (3 cycles)	Arm 1: neoadjuvant CTX (3 cycles) Arm 2: adjuvant CTX (3 cycles)	Neoadjuvant CTX (3 cycles)	Neoadjuvant nivolumab+ platinum-doublet CTX (3 cycles)	Neoadjuvant pembrolizumab+cisplatin--doublet CTX (4 cycles) followed by surgery and adjuvant pembrolizumab (13 cycles)
Platinum doublet chemotherapy options	Gemcitabine plus cisplatin	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin	Non-squamous disease: platinum+pemetrexed Squamous disease: platinum+gemcitabine/ vinorelbine/docetaxel	Non-squamous disease: cisplatin+carboplatin Squamous disease: cisplatin+gemcitabine
Comparator	Surgery alone	Surgery alone	Surgery alone	Neoadjuvant platinum-doublet chemotherapy (3 cycles)	Neoadjuvant cisplatin-based -doublet chemotherapy (4 cycles)
Median follow-up	3.3 years (chemo plus surgery); 2.6 years (surgery) Trial terminated early	51 months	64 months Trial terminated early	29.5 months	29.8 months
Outcome	PFS	DFS	PFS	EFS	EFS
Risk of bias[24]	Some concerns	Some concerns	Some concerns	Some concerns	Low

AJCC=American Joint Committee on cancer; CTX=chemotherapy; DFS=disease-free survival; EFS=event-free survival; NSCLC=non-small cell lung cancer; PFS=progression-free survival
Source: adapted from CS, Table 21

3.7.3 Quality assessment of trials included in the NMAs

For the RCTs included in the company NMAs, the company used the Cochrane RoB2[24] tool to assess the risk of bias for the EFS, DFS and PFS outcomes. Results of the company's assessments are presented in

Table 13. The EAG agrees with the company that open label trials[19-22] carry a risk of subjectivity and also that any subjectivity in the CheckMate-816[22] trial is likely to be mitigated, as EFS was assessed by blinded independent review.

Table 13 Company's assessment of risk of bias of RCTs included in the NMAs

Trials	D1	D2	D3	D4	D5	Overall
CHEST[21]	!	!	!	+	+	Some concerns
CheckMate-816[22]	+	!	+	+	+	Some concerns
Felip 2010[19]	+	!	+	+	+	Some concerns
Pisters 2010[20]	+	!	+	+	+	Some concerns
KEYNOTE-671[17]	+	+	+	+	+	Low risk

! =some concerns of bias; + =low risk of bias; NMA=network meta-analysis
D1=randomisation process; D2=deviations from the intended interventions; D3=missing outcome data; D4=measurement of the outcome; D5=selection of the reported result
Source: CS, Appendix D, Table 12

3.7.4 NMA methodology: time constant and time-varying NMAs

Outcomes

The company performed EFS NMAs only. The company decided not to perform OS NMAs as the OS data from the relevant RCTs were considered immature. As it was not possible to draw firm conclusions from the available direct evidence, the company concluded that results from OS NMAs would also be uncertain (CS, p64). The EAG accepts the company's rationale for not conducting AE, HRQoL and pCR NMAs (see company response to clarification question A2).

To conduct the EFS NMAs, the company assumed that DFS (Felip 2010[19]), PFS (CHEST[21] trial and Pisters 2010[20]) and EFS (KEYNOTE-671[17]and CheckMate-816[22] trials) were similar outcomes. Clinical advice to the EAG is that this assumption is reasonable. Definitions for each of these outcomes are provided in the CS (CS, Appendix D, Table 11).

The company conducted NMAs for both investigator-assessed and BICR-assessed EFS. However, data for both investigator-assessed and BICR-assessed EFS were only available from the KEYNOTE-671[17] trial; thus, only KEYNOTE-671[17] trial outcomes differ between the investigator-assessed and BICR-assessed EFS analyses. BICR-assessed EFS data are only available from the CheckMate-816[22] trial; method of DFS or PFS assessment was not reported in the main publications for the remaining three[19-21] trials.

Network of evidence

Five relevant RCTs[17,19-22] facilitated the generation of a connected EFS network of evidence (Figure 2).

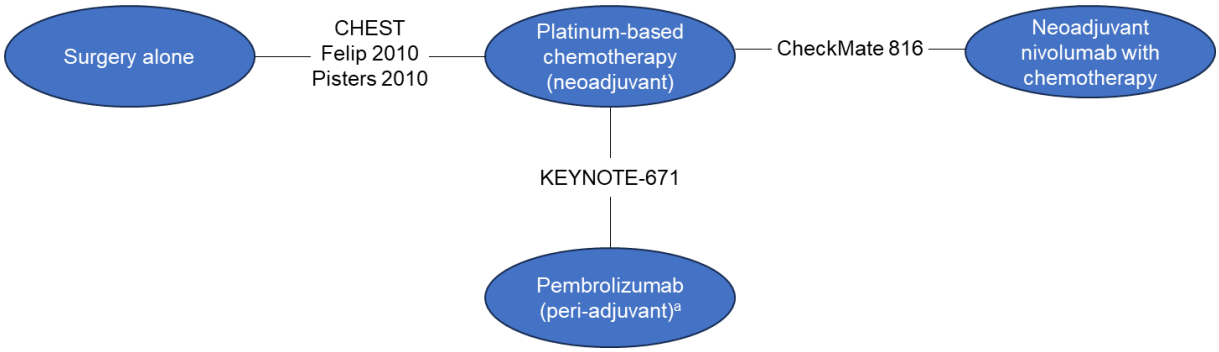

Figure 2 Network of EFS evidence

[a] Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab monotherapy
EFS=event-free survival
Source: Adapted from CS, Figure 12

To generate this network of evidence, the company made the following assumptions:

- cisplatin plus gemcitabine and cisplatin plus pemetrexed have similar clinical efficacy
- treatments pooled within each node have similar clinical efficacy
- no adjuvant treatment is equivalent to receiving placebo in the adjuvant setting

Clinical advice to the EAG is that these assumptions are reasonable.

Time-constant versus time-varying HRs

In the company's time-constant HR EFS NMAs, the treatment effect for each comparison is estimated by a HR and 95% credible interval (CrI), which are assumed to remain constant over time. Data inputs for the time-constant HR EFS NMAs were sourced from the five[17,19-22] included RCT publications. The reliability of time-constant HR EFS NMA results depends on the assumption that, for each included RCT, event hazards associated with the intervention and comparator are proportional over time. For each RCT, the company assessed the assumption of proportional hazards (PH) using standard statistical tests; in the CS, the company stated that the standard tests used to evaluate the assumption are underpowered to detect all but the most pronounced violations of proportional hazards[31]" (CS, p70) and carried out time-varying HR EFS NMAs.

The company also presented additional results from an investigation of KEYNOTE-671[17,19-22] and CheckMate-816[22] immunotherapy trials hazards over time (CS, Figure 13). The company fitted exponential, Weibull and Gompertz distributions to KEYNOTE-671[17] trial individual patient data (IPD) and CheckMate-816[22] pseudo-IPD data (generated using the Guyot

algorithm[32] from trial Kaplan-Meier [K-M] curves; company response to clarification question A3).

Based on AIC values (CS, Appendix D, Table 25) and a visual inspection of fit to the observed data (CS, Appendix D, Figure 8 to Figure 10), the company determined that the Gompertz distribution was the most appropriate distribution to use to model KEYNOTE-671[17] and CheckMate-816[22] trial EFS HRs over time. The company observed that [redacted] (CS, p71). The company also highlighted that "[redacted]."

The company considered that it was biologically plausible that HRs would vary across the network of evidence (for example, due to differences in timing of surgery), meaning that time-varying HR EFS NMAs were more appropriate than time-constant HR EFS NMAs (CS, p71).

3.7.5 Company EFS NMA methods

Time-constant HR EFS NMAs

Time-constant HR EFS NMAs were conducted using a Bayesian framework. The company used a regression model with a contrast-based normal likelihood for the log HR (and corresponding standard error) of each trial (or comparison) in the network.

Time-varying HR EFS NMAs

Time-varying HR EFS NMAs were conducted using a Bayesian framework and the model introduced by Jansen.[33] For each comparator trial, the company generated pseudo-IPD from published K-M curves using the Guyot algorithm[32] to obtain datasets that could be used in the NMAs. The company explained (response to clarification question A1) that the hazard functions of the interventions in each trial were modelled using known parametric survival functions or fractional polynomials (Weibull, Gompertz and second order fractional polynomials including p1=0 or 1 and p2= -1, -0.5, 0, 0.5 or 1). For the relative treatment effects in the second order fractional polynomial framework, the company assessed models which assumed: i) treatment only has an impact on two of the three parameters describing the hazard function over time (i.e., one scale and one shape parameter), and ii) treatment has an impact on all three parameters describing the hazard function over time (i.e., one scale and two shape parameters). The company considered the deviance information criterion (DIC) and plausibility of the estimated time-varying HRs when selecting the most appropriate survival model.

Fixed-effects versus random-effects models

The company presented results from both fixed-effects and random-effects models for both the time-constant and the time-varying HR EFS NMAs. The company tested model fit by examining the DIC and deviation at the posterior mean of the model.

3.7.6 NMA results

Time-constant HR EFS NMAs

The company stated that model fit test (DIC and deviation) results indicated that fixed-effects models provided a better fit to the data than random-effects models (CS, p79).

A summary of company time-constant HR EFS NMA results (fixed-effects model and random-effects model) is provided in Table 14. The EAG has not presented results for periadjuvant pembrolizumab versus neoadjuvant chemotherapy in the main body of this report as clinical advice to the EAG is that neoadjuvant chemotherapy is not a relevant comparator; for completeness, summary results are presented in Appendix 8.1 (Table 44 and Table 45).

Table 14 Summary of company **time-constant** HR EFS NMA results (fixed-effects model and random-effects model)

Analysis	HR (95% CrI)	
	Periadjuvant pembrolizumab versus surgery alone	**Periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy**
Fixed-effects	0.52 (0.41 to 0.65)	0.87 (0.59 to 1.27)
Random-effects	0.49 (0.09 to 2.56)	0.87 (0.10 to 7.27)

CrI=credible interval; EFS=event-free survival; HR=hazard ratio; NMA=network meta-analysis
Source: CS, Table 22

For the comparison of periadjuvant pembrolizumab versus surgery alone, the fixed-effects model HR indicates a statistically significant treatment effect in favour of periadjuvant pembrolizumab. The random-effects model HR is very similar to the fixed-effects model HR; however, the random-effects model 95% CrI is much wider than the fixed-effects model 95% CrI and the treatment effect is no longer statistically significant.

For the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy, the fixed-effects model HR and the random-effects model HRs are identical and favour periadjuvant pembrolizumab; however, these results are not statistically significant and the random-effects model 95% CrI is wide (0.10 to 7.27).

Company time-constant HR BICR-assessed EFS NMA fixed-effects and random-effects results were very similar to investigator-assessed EFS NMA fixed-effects and random-effects results (CS, Appendix D, Table 23 and Table 24).

Time-varying HR NMAs

The company considered that the Weibull distribution, with an additional shape parameter (P1=0, P2=-0.5), was the most appropriate distribution to use to model investigator-assessed EFS time-varying HR NMAs. The company states (CS, p72) that, "…tests assessing model fit indicated no meaningful difference between random and fixed effects models" for the time-varying HR NMAs, and that "fixed effect models are the most appropriate for decision-making".

A summary of time-varying HR investigator-assessed EFS NMA results (Weibull model with 2nd shape parameter, P1=0 P2=-0.5, fixed-effects model and random-effects model) is provided in Table 15. The EAG has not presented results for periadjuvant pembrolizumab versus neoadjuvant chemotherapy in the main body of this report as clinical advice to the EAG is that neoadjuvant chemotherapy is not a relevant comparator; for completeness, summary results are presented in Appendix 8.1 (Table 44 and Table 45).

Table 15 Summary of **time-varying** HR EFS NMAs (fixed-effects model and random-effects model) for the outcome of investigator-assessed EFS (periadjuvant pembrolizumab versus relevant comparators, Weibull model with 2nd shape parameter, P1=0 P2=-0.5)

Comparator	Time-varying HR (95% CrI)											
	Time in months											
	3	6	9	12	18	24	30	36	42	48	54	60
Fixed-effects model												
Surgery alone	**0.49 (0.33 to 0.71)**	**0.48 (0.37 to 0.62)**	**0.48 (0.37 to 0.62)**	**0.48 (0.37 to 0.63)**	**0.48 (0.35 to 0.65)**	**0.48 (0.34 to 0.66)**	**0.48 (0.34 to 0.67)**	**0.48 (0.33 to 0.68)**	**0.48 (0.33 to 0.69)**	**0.48 (0.32 to 0.70)**	**0.48 (0.32 to 0.71)**	**0.48 (0.32 to 0.71)**
Neoadjuvant nivolumab with chemotherapy	1.30 (0.72 to 2.36)	0.97 (0.66 to 1.43)	0.85 (0.58 to 1.24)	0.79 (0.53 to 1.18)	0.72 (0.46 to 1.13)	0.68 (0.42 to 1.12)	0.66 (0.39 to 1.11)	0.64 (0.37 to 1.10)	0.63 (0.36 to 1.10)	0.61 (0.34 to 1.10)	0.61 (0.33 to 1.10)	0.60 (0.33 to 1.10)
Random-effects model												
Surgery alone	0.47 (0.14 to 1.39)	0.47 (0.14 to 1.36)	0.48 (0.14 to 1.36)	0.48 (0.14 to 1.37)	0.48 (0.14 to 1.37)	0.48 (0.14 to 1.36)	0.48 (0.14 to 1.37)	0.48 (0.14 to 1.37)	0.48 (0.14 to 1.38)	0.48 (0.14 to 1.38)	0.48 (0.14 to 1.39)	0.48 (0.14 to 1.39)
Neoadjuvant nivolumab with chemotherapy	1.26 (0.31 to 4.60)	0.96 (0.24 to 3.27)	0.85 (0.21 to 2.90)	0.79 (0.20 to 2.70)	0.72 (0.18 to 2.48)	0.68 (0.17 to 2.35)	0.66 (0.16 to 2.28)	0.64 (0.15 to 2.25)	0.63 (0.15 to 2.21)	0.62 (0.15 to 2.19)	0.61 (0.14 to 2.17)	0.61 (0.14 to 2.15)

Cells shaded in grey indicate estimates based on model extrapolations
All **bolded** values are statistically significant at the 0.05 significance level
CrI=credible interval; HR=hazard ratio; EFS=event-free survival; NMA=network meta-analysis
Source: CS, Table 25 and Table 26

For the comparison of periadjuvant pembrolizumab versus surgery alone, the fixed-effects model HRs indicate a statistically significant treatment effect in favour of periadjuvant pembrolizumab at all time-points. The random-effects model HRs are very similar to the fixed-effects model HRs but the 95% CrIs are wider and, at all time-points, the treatment effect is not statistically significantly different.

For the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy, the fixed-effects model HRs and the random-effects model HRs favour neoadjuvant nivolumab with chemotherapy at 3 months and favour periadjuvant pembrolizumab at all subsequent time points. However, none of the observed treatment effects are statistically significantly different, and the random-effects model generates particularly wide 95% CrIs.

The company determined that the Weibull distribution, with an additional shape parameter (P1=0, P2=0), was the most appropriate distribution to use to generate BICR-assessed EFS time-varying HR EFS NMAs. BICR-assessed EFS NMA results were similar to investigator-assessed EFS NMA results (CS, Appendix D, Table 16 and Table 17).

3.7.7 EAG comments on company NMAs

Time-constant HR NMAs

To assess the reliability of company time-constant HR EFS NMA results, the EAG asked the company to provide results from all PH assessments (clarification question A6). Grambsch & Therneau test and Wald test results suggest that the PH assumption may be violated for two[19,20] trials. Although the EAG considers that some of the presented graphs are difficult to interpret, the EAG agrees with the company that formal PH violation test results are not statistically significant for the two main trials (KEYNOTE-671[17] and CheckMate-816[22] trials), or for CHEST.[21] Therefore, the EAG considers that the methods used by the company to conduct time-constant HR EFS NMAs were appropriate and that these NMA results can be used to inform decision-making.

In this appraisal, based on available data, choosing between a fixed-effects and random-effects model is challenging. The appropriateness of fixed-effects or random-effects models should be made based on consideration of clinical and methodological heterogeneity across trials. The fixed-effect model assumes that there is one true effect size that underlies each of the comparisons in the network and that all differences in the observed effect sizes are due to sampling error. The random effects model assumes that the true effect could vary from study to study because of clinical and methodological heterogeneity. Due to heterogeneity in the evidence base (for example, proportion of patients with squamous cell disease, see Section

3.7.2 of this report), the EAG considers that the assumption underlying the random-effects model is more plausible than the assumption underlying the fixed-effects model. However, the EAG also notes that data included in the company's NMAs were sparse, with only one trial contributing data to the comparisons of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy and versus neoadjuvant chemotherapy. When data are sparse, the heterogeneity parameter for the random-effects model may be very imprecisely estimated (leading to instable estimates of HR standard errors and consequently to wide 95% CrIs). The company considered that results from fixed-effect models were more informative than results from random-effects models. The EAG considers that results from the fixed-effects model provide the most robust results; however, given the weaknesses of the fixed-effects and random-effects models, it is reasonable for the company to present both sets of time-constant HR EFS NMA results.

Time-varying HR NMAs

The EAG acknowledges the limitations of the standard tests for assessing PH. However, the EAG does not consider that the company has provided a sufficiently strong rationale to support the view that time-varying HR EFS NMA results are more informative than time-constant HR EFS NMA results.

Clinical advice to the EAG is that, for the treatment comparisons included in the company's network of evidence, a time varying treatment effect is plausible but its existence, magnitude and duration are associated with uncertainty, given the available data. In addition, the EAG considers that the reliability of the company's time-varying HR NMAs results is uncertain due to the subjective nature of the model selection process. The company fitted 22 models for investigator-assessed EFS and 22 models for BICR-assessed EFS (company response to clarification question A1). The company explained that selection of the best-fitting fixed effects and random effects models was based on lowest DIC, followed by visual inspection to compare the lowest DIC models with trial K-M curves to confirm that these models were plausible. Whilst the use of DIC is objective, the choice of which and how many models to fit is subjective, further, visual inspection against trial K-M curves is also subjective and is prone to both confirmation bias and researcher bias.

Furthermore, use of the methods described by Jansen[33] to estimate company models means that the width of the 95% CrIs around the time-varying HRs remains approximately the same at all time points. The 95% CrIs do not reflect the number of patients providing data at each time point (which diminishes over time); rather, they reflect the amount of data available overall. The EAG does not consider that it is appropriate to infer statistical significance (or lack of statistical significance) from time-varying HR NMA 95% CrIs. The time varying HR models

therefore do not provide robust statistical evidence to support a hypothesis that the EFS HRs change over time. The EAG is not aware of existing methods that can be used to adjust time-varying HR NMA 95% CrIs to reflect the number of patients providing data at each timepoint.

3.7.8 EAG concluding remarks

For the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy, all company time-constant and time-varying HR EFS NMA results suggest that there are no statistically significant differences between the two treatments; this means that there is insufficient statistical evidence to conclude that, in terms of EFS, periadjuvant pembrolizumab is more clinically effective than neoadjuvant nivolumab with chemotherapy. The EAG highlights that, as there is no evidence that the PH assumption was violated in either the KEYNOTE-671[17] trial or in theCheckMate-816[22] trial, the company time-constant EFS HR results can be used to inform decision making.

For the comparison of periadjuvant pembrolizumab versus surgery, company time-constant and time-varying fixed-effects HR EFS NMA results show that periadjuvant pembrolizumab is statistically significantly more effective than surgery; however, results from the time-constant and time-varying random-effects HR EFS NMA are not statistically significant.

The EAG considers that all time-varying HR EFS NMA results should not be used to draw conclusions about the relative effectiveness of periadjuvant pembrolizumab versus nivolumab with chemotherapy and versus surgery. All time-varying HR EFS NMA results should be considered as speculative and of limited use to inform decision-making.

3.8 EAG clinical effectiveness conclusions

3.8.1 Decision problem

Comparators

The company considered that four of the comparators listed in the final scope issued by NICE (periadjuvant durvalumab, adjuvant osimertinib, atezolizumab and neoadjuvant chemoradiotherapy) were not relevant comparators. At clarification, NICE asked the company to provide clinical and cost effectiveness evidence for the comparison of periadjuvant pembrolizumab versus periadjuvant durvalumab and versus adjuvant osimertinib. In the clarification response, the company outlined their reasons for not providing this evidence and made suggestions about how this evidence could be incorporated into the NICE process if these treatments were to be recommended by NICE for routine commissioning prior to the first NICE AC meeting for periadjuvant pembrolizumab.

3.8.2 Direct evidence

The KEYNOTE-671 trial is a well-conducted trial that provides statistically significant results in favour of periadjuvant pembrolizumab versus neoadjuvant chemotherapy. The EAG is satisfied that the methods used to analyse KEYNOTE-671 trial results were appropriate. Trial results demonstrate a statistically significant EFS benefit for patients treated with periadjuvant pembrolizumab compared to patients in the placebo arm. There were no differences in HRQoL between trial arms. Periadjuvant pembrolizumab was shown to have a manageable toxicity profile and no new safety concerns were identified.

Clinical advice to the company was that treatment would likely be stopped for patients who achieve pCR after surgery. Therefore, the relevance of the trial results to NHS patients is uncertain. In addition, it is unclear how clinicians will determine which patients are likely to benefit most from post-surgery immunotherapy. Further, clinical advice to the EAG is that KEYNOTE-671 trial patients are considerably younger (mean=63.1 years) than NHS patients (average age of 70 years) and that older, less fit NHS patients may not be suitable for treatment with immunotherapy treatment.

3.8.3 Indirect evidence

The company has only generated indirect evidence for a single outcome (EFS); the EAG considers that, given the available evidence, this approach is appropriate. KEYNOTE-671 trial periadjuvant pembrolizumab OS data are not informative as there have been few events; the immaturity of trial OS data mean that it is not currently possible to generate reliable indirect OS NMA results for the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy (the most relevant comparator).

The company carried out time-constant and time-varying HR EFS NMAs using fixed-effects and random-effects models. The EAG considers that the methods used by the company to conduct time-constant HR EFS NMAs were appropriate and that fixed-effects models provide more robust results than random-effects models. The EAG considers that all company time-varying HR EFS NMA results should be considered speculative and are of limited use to decision making. The EAG does not consider that the company has provided a sufficiently strong rationale to support their view that time-varying HR EFS NMA results are more informative than time-constant HR EFS NMA results.

Company EFS NMA results

The EAG considers that neoadjuvant nivolumab with chemotherapy is the most relevant comparator. Company time-constant and time-varying (fixed-effects and random-effects) HR EFS NMA results show that there is insufficient evidence to conclude that periadjuvant treatment with pembrolizumab confers a statistically significant clinical benefit compared with neoadjuvant nivolumab with chemotherapy.

Company time-constant (fixed-effects and random-effects) and time-varying fixed-effects HR EFS NMA results show that periadjuvant pembrolizumab confers a statistically significant clinical benefit compared with surgery alone.

4 COST EFFECTIVENESS EVIDENCE

This section provides a summary of the economic evidence submitted by the company in support of the use of periadjuvant pembrolizumab (neoadjuvant pembrolizumab in combination with platinum chemotherapy followed by adjuvant pembrolizumab) as a treatment option for adults with early-stage previously untreated resectable NSCLC at high risk of recurrence. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft® Excel.

4.1 Company review of published cost effectiveness evidence

The company undertook a SLR to identify and appraise i) published cost effectiveness evaluations ii) HRQoL data and iii) healthcare resource use and cost data relevant to the decision problem. The SLR target population was broadly defined as adults with early-stage resectable NSCLC with no specific restrictions by disease stage or tumour size. Economic evaluations were restricted to those evaluating systemic therapies administered in any setting (neoadjuvant, periadjuvant/peri-operative or adjuvant).

Electronic database searches were originally conducted in February 2023 to identify studies published from April 2012 onwards, with the latest update conducted in November 2023. No language restriction was specified in the searches but only studies reporting in English were included in the review. The company also searched conference proceedings to identify abstracts published between January 2021 and March 2023. Searches of Health Technology Assessment agency websites and the bibliographies of any identified SLRs and economic evaluations were conducted. Full details of the methods used by the company to identify and select relevant cost effectiveness evidence are presented in the CS (Appendix G, Appendix H and Appendix I).

The company identified 31 unique economic evaluations that assessed interventions for patients with early-stage resectable NSCLC. Of these, seven studies were conducted from a UK perspective (one in the neoadjuvant setting and six in the adjuvant setting). The economic evaluation carried out in the neoadjuvant setting was a NICE technology appraisal of nivolumab with chemotherapy(TA876[11]) and the six economic evaluations in the adjuvant setting evaluated atezolizumab (TA823,[12] SMC,[34] and Yip[35]) and osimertinib (TA761,[7] SMC,[36] and Bracke[37]). Four HRQoL studies were identified: one study[38] reported HRQoL data for patients in the neoadjuvant setting, two studies[39,40] reported HRQoL data for patients in the adjuvant setting, and the remaining study[41] reported HRQoL estimates for patients with

NSCLC across different stages and treatment strategies. The company SLR identified 17 resource use and/or cost studies; however, only one study[39] reported cost and resource use data in a UK setting.

4.2 EAG critique of company literature review

The EAG considers all the company's cost effectiveness evidence SLR methods were of a good standard (Table 16). The company's database searches were comprehensive and search terms included a good combination of index terms and free-text words relevant to the disease area.

Table 16 EAG appraisal of systematic review methods

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Not reported
Was data extracted by two or more reviewers independently?	Not reported
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Yes
Were attempts to synthesise evidence appropriate?	Yes

EAG=External Assessment Group; HRQoL=health-related quality of life; LR*i*G=Liverpool Reviews and Implementation
Source: LR*i*G in-house checklist

4.2.1 EAG conclusion

The EAG considers the methods used to conduct the company's systematic reviews of cost effectiveness evidence, HRQoL and healthcare resource use studies were of a good standard.

4.2 EAG summary and critique of the company's submitted economic evaluation

4.2.1 NICE Reference Case checklist and Drummond checklist

Table 17 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	Yes
Comparators	As listed in the scope developed by NICE	Partial. The company has only provided cost effectiveness results for the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy, surgery alone and neoadjuvant chemotherapy
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
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	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Source: EAG assessment of NICE Reference Case[42]

Table 18 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	The only comparative clinical effectiveness evidence provided by the company was generated by company EFS NMAs for three/seven comparators listed in the final scope issued by NICE
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

EAG=External Assessment Group; EFS=event-free survival; NMA=network meta-analysis
Source: Drummond and Jefferson[43]

4.3 Model structure

The company developed a de novo Markov cohort model in Microsoft® Excel to evaluate the cost effectiveness of periadjuvant pembrolizumab for treating adult patients with resectable Stage II, IIIA or IIIB (T3-4N2) NSCLC. The model consists of four mutually exclusive health states: event-free, local-regional recurrence or progression (LR/P), distant metastasis (DM) and death. LR/P and DM are both recurrence events included within the event-free outcome (the KEYNOTE-671 trial primary endpoint); however, they are each associated with different health outcomes and costs and therefore have been modelled using separate health states. Patients enter the model in the event-free health state and treatment affects patients' risk of transitioning from event-free to LR/P, DM or death, as well as the probability of receiving initial surgery. The company has assumed that once a patient has progressed to the LR/P state, transition probabilities are equivalent across treatment arms (i.e., the treatment effect of periadjuvant pembrolizumab only related to the event-free health state). Transition probabilities from the DM health state are equivalent across treatment arms for patients with the same immunotherapy eligibility status. An illustration of the company model structure is presented in Figure 3.

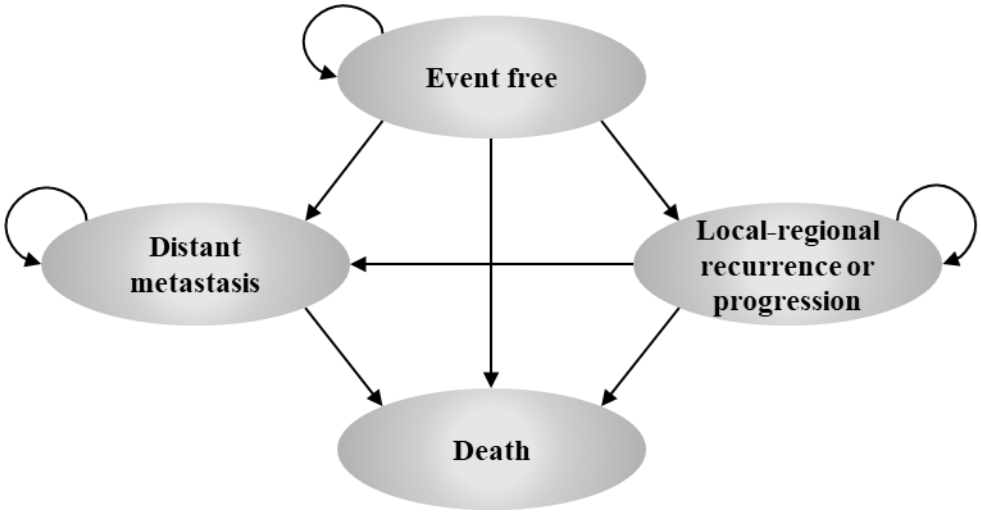

Figure 3 Company model structure

Source: CS, Figure 15

4.4 Population

The company defined the population of interest as adults with resectable Stage II, IIIA or IIIB (T3/4N2) NSCLC; this is in line with the MHRA marketing authorisation[9] for periadjuvant pembrolizumab. The baseline parameters used in the company model reflect KEYNOTE-671 trial patient baseline characteristics (Table 19). Body surface area, weight, and glomerular filtration rate were used in the model to estimate the required doses of some subsequent treatments in the metastatic NSCLC setting. The glomerular filtration rate used in the company model was the same rate that was used in a prior NICE appraisal of pemetrexed (TA181[44]).

Table 19 Model population characteristics

Characteristics	Value	Source
Starting age (years), mean	[redacted]	KEYNOTE-671 trial
Proportion of female patients, %	[redacted]	
Body surface area (m^2), mean	[redacted]	
Body weight (kg), mean	[redacted]	
Squamous histology (%)	43.2	
Non-squamous histology (%)	56.8	
Glomerular filtration rate (mL/min/1.73m^2)	75.0	TA181[44]

Source: CS, Table 37

4.5 Interventions and comparators

Pembrolizumab

In the **neoadjuvant setting**, patients received pembrolizumab plus chemotherapy:

- pembrolizumab (maximum four cycles): fixed dose of 200mg Q3W (KEYNOTE-671 trial dosing regimen)
- chemotherapy (four cycles)

- squamous histology: cisplatin (75mg/m^2) plus gemcitabine 1,000mg/m^2 Q3W
- non-squamous histology: cisplatin (75mg/m^2) plus pemetrexed (500mg/m^2) Q3W

In the **adjuvant setting**, patients in the KEYNOTE-671 trial received pembrolizumab monotherapy at a fixed dose of 200mg Q3W for a maximum of 13 cycles or until disease recurrence, toxicities leading to discontinuation, or physician/patient decision. Pembrolizumab can also be administered at a fixed dose of 400mg Q6W.

Clinical advice to the company was that, in the adjuvant setting, clinicians would prefer to use the Q6W dosing regimen. The company has therefore assumed that, in the adjuvant setting, patients receive one cycle of pembrolizumab 200mg, followed by a 400mg dose Q6W for a maximum of six cycles.

Comparator treatments

The comparators included in the company model are neoadjuvant chemotherapy, neoadjuvant nivolumab with chemotherapy and surgery alone. Neoadjuvant chemotherapy was modelled based on the treatments administered to KEYNOTE-671 trial comparator arm patients (Table 20). All comparator drugs are administered via IV infusion.

Table 20 Comparator treatment regimens included in the company model

Treatment	Component	Dosing	Frequency	Maximum number of treatment cycles
Neoadjuvant pembrolizumab plus chemotherapy KEYNOTE-671 trial	Pembrolizumab	200mg	Q3W	4
	Cisplatin	75mg/m^2		
	Gemcitabine (squamous)	1000mg/m^2 on days 1 and 8 of 3-week cycles		
	Pemetrexed (non-squamous)	500mg/m^2		
Adjuvant pembrolizumab KEYNOTE-671 trial	Pembrolizumab	First dose: 200mg Subsequent doses: 400mg	First dose: Q3W Subsequent doses: Q6W	6
Neoadjuvant nivolumab with chemotherapy CheckMate-816 trial[22]	Nivolumab	360mg	Q3W	3
	Carboplatin	AUC 5 or 6mg/ml/min		
	Cisplatin	75mg/m^2		
	Gemcitabine (squamous)	1000 or 1250mg/m^2 on days 1 and 8 of 3-week cycles		
	Pemetrexed (non-squamous)	500mg/m^2		
	Paclitaxel	175 or 200mg/m^2		

AUC=area under the curve; IV=intravenous; Q3W=every 3 weeks; Q6W=every 6 weeks
Source: CS, Table 54

4.6 Perspective, time horizon and discounting

The model perspective was reported as NHS and Personal Social Services (PSS). The model cycle length was 1 week, and a half-cycle correction was applied to health outcomes and costs, excluding events that occur at the beginning of a model cycle (e.g., drug acquisition and administration costs, AE-related costs and disutilities). The model time horizon, which was based on the mean age of patients at the start of the KEYNOTE-671 trial (63.1 years), was 36.9 years, and costs and outcomes were discounted at a rate of 3.5% per annum.

4.7 Treatment effectiveness and extrapolation

4.7.1 Transitions from the event-free health state

Periadjuvant pembrolizumab and neoadjuvant chemotherapy

Transition probabilities from the event-free health state were estimated using parametric distributions fitted to KEYNOTE-671 trial EFS patient-level data (IA2 data cut: 10th July 2023). The company followed the parametric multi-state modelling approach described by Williams[45,46] to estimate the cause-specific hazard of each possible transition from the event-free health state over time. Since EFS failure encompasses three different events (LR/P, DM or death), additional censoring was applied to the EFS data to account for competing risks (e.g., to model the transition from EF to DM, patients who experience a LR/P or death prior to DM were censored at the time of the earlier competing event). After applying this additional censoring, seven standard parametric distributions (exponential, Weibull, Gompertz, lognormal, loglogistic, gamma and generalised gamma) were fitted to patient level EFS data. For each specific type of EFS failure, the estimated cumulative hazard was converted into a weekly transition probability (CS, p110).

The company explored three different approaches to estimating cause-specific hazards from the event-free health state:

1. parametric distributions fitted independently to each treatment arm
2. parametric distributions fitted jointly with binary variable for treatment arm (assuming proportional hazards)
3. parametric distributions fit jointly with binary variables for treatment arm *and* follow-up before/after 1 year (varying HR before and after 1 year)

Since seven parametric distributions were considered for each of the three cause-specific hazards, using Approach 1 generates 343 possible combinations of parametric distributions (the company assumed the same distribution is used to estimate cause-specific hazards for both treatment arms). Approaches 2 and 3 use jointly fitted parametric models and each generates 27 possible combinations, resulting in a total of 397 possible combinations.

When selecting base case parametric distributions, the company considered the following:

- statistical fit
- assessment of the PH assumption
- visual assessment of fit
- clinical plausibility of long-term extrapolations

Based on statistical fit, the company considered that, for the neoadjuvant chemotherapy arm combinations, modelling the EF→death transition using the lognormal distribution under Approach 1, and the Gompertz distribution under Approaches 2 and 3, produced the lowest mean standard errors (MSEs). The company therefore assessed the visual fit of the 67 combinations that used these distributions to model the hazard of death in the EF health state.

The company excluded 49 combinations of parametric distributions based on visual fit. Of the 18 combinations remaining, one ranked in the bottom 50% by MSE in both arms and was therefore excluded.

Although the PH assumption could only be rejected for the EF→Death transition, the company preferred to fit parametric distributions independently for all transitions, and therefore excluded one combination that used Approach 2.

Long-term predictions of EFS and OS did not substantially vary across the remaining 16 combinations and so the company's assessment of clinical plausibility focused on the eight combinations that were in the top 10 best-fitting distributions for both arms. Across all eight combinations, the estimated incremental EFS benefit of periadjuvant pembrolizumab versus neoadjuvant chemotherapy was closely aligned with the observed EFS benefit in the KEYNOTE-671 trial, whilst the observed incremental OS benefit was underpredicted.

The company selected the generalised gamma to model the hazard of progression to LR/P and DM for both treatment arms (Table 21). Of the original 397 candidate combinations, this combination was the best-fitting in the neoadjuvant chemotherapy arm and the 5th best-fitting in the pembrolizumab arm.

Table 21 Company base case parametric distributions used to model transition probabilities from the event-free health state to other health states for patients treated with periadjuvant pembrolizumab or neoadjuvant chemotherapy

Company base case	Transition		
	EF→LR/P	EF→DM	EF→death
Parametric distribution	Generalised gamma	Generalised gamma	Lognormal

DM=distant metastasis; EF=event-free; LR/P=loco-regional recurrence or progression
Source: CS, Table 40

In each model cycle, transition probabilities to death from all health states were constrained by age- and sex-matched mortality rates from the general population; these were sourced from ONS life tables.[47]

Neoadjuvant nivolumab with chemotherapy and surgery alone

For patients treated with neoadjuvant nivolumab with chemotherapy or surgery alone, transition probabilities from the event-free health state were estimated by applying company time-varying HRs (Weibull, fixed-effects model) to the overall hazard of any EFS failure for patients treated with periadjuvant pembrolizumab. To obtain the cause-specific hazards for each transition (i.e., event-free→LR/P, event-free→DM and event-free→death), the company assumed that the proportion of the overall hazard attributable to each EFS failure type was the same as that for patients treated with periadjuvant pembrolizumab. The HR used beyond 5.2 years (latest KEYNOTE-671 trial data cut maximum follow-up) was held constant.

Cure point

In the company model, a proportion (95%) of patients who remain event-free after 5 years are considered cured. For the patients who remain in the event-free health state for ≥5 years, the probability of recurrence or progression (to either the LR/P health state or DM health state) is set to zero and the probability of death is set equal to background mortality. Between 5 years and the end of 7 years, the cure proportion increases from 0% to 95% to prevent a visible kink in the EFS curve. The company considered that this modelling approach was consistent with approaches undertaken in previous appraisals.[7,11,12] This approach was supported by clinical advice[48] to the company that most relapses occur in the first 5 years and there are very few, if any, recurrences or disease-related deaths after 5 years.

4.7.2 Transitions from the LR/P health state

In the KEYNOTE-671 trial, follow-up imaging data were not routinely collected for patients who experienced LR/P as their first event. Therefore, the company used external data sources to estimate the probability of transitioning from the LR/P health state to the DM health state or the death health state. The company matched real-world data from the US SEER-Medicare administrative claims and linked cancer registry database to KEYNOTE-671 trial patient baselined characteristics (CS, Appendix M.2); 221 patients were identified and, of these, 43 were identified as having a local-regional recurrence/progression at least 30 days prior to any metastatic occurrence.

The company fitted exponential competing risk models to the time to event data using the same censoring approach used to estimate transition probabilities from the event-free health state to other health states. The exponential distribution was chosen to minimise the

computational burden and complexity of the model; this distribution is only appropriate if it is valid to assume that hazards remain constant over time. The company constrained the transition probability from the LR/P health state to the death health state so that it was at least as high as background mortality in each weekly cycle. The cause-specific hazards for each transition from the LR/P health state are presented in Table 22.

Table 22 Parameters used to model transition probabilities from the LR/P health state to the DM health state and the death health state

Data source	LR/P→DM		LR/P→death	
	Weekly exponential rate	SE	Weekly exponential rate	SE
SEER Medicare KEYNOTE-671 trial-matched cohort (per weekly cycle)	[redacted]	[redacted]	[redacted]	[redacted]

DM=distant metastases; LR/P=local-regional recurrence or progression; SE=standard error
Source: CS, Table 43

4.8 Scenario analyses

The company conducted scenario analyses exploring alternative model assumptions and alternative estimates of parameter values. Cost effectiveness results for the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy were most sensitive to the scenarios that used results from alternative NMA models (Company response to clarification question B6, Table 11).

4.8.1 Transitions from the DM health state

For each modelled treatment, transition probabilities from the DM health state were assumed to depend on the distribution and expected survival of patients receiving first-line treatments for metastatic NSCLC. Although the company model includes the cost of second-line treatment for metastatic NSCLC, survival only varies by first-line metastatic treatment.

The proportions of patients in the company model who receive each first- and second-line metastatic NSCLC treatment were derived based on clinical advice, the prevalence of different mutation/expression types in the population and simplifying assumptions. The company assumed that no patients were contraindicated to treatment with an immunotherapy.

First-line treatments

The company defined patients who were ineligible or eligible for first-line treatment with immunotherapies in the metastatic setting using the following criteria:

- **immunotherapy-eligible**: patients who had never received periadjuvant pembrolizumab or neoadjuvant nivolumab with chemotherapy (i.e., neoadjuvant chemotherapy and surgery alone arms) or who transitioned to the DM health state at least 6 months after the final scheduled dose of immunotherapy (periadjuvant pembrolizumab arm: 21 months after the start of the model; neoadjuvant nivolumab with chemotherapy arm: 8 months after the start of the model)

- **immunotherapy-ineligible**: patients in the periadjuvant pembrolizumab or neoadjuvant nivolumab with chemotherapy arms who transition to the DM health state within 6 months of the final scheduled dose of immunotherapy (periadjuvant pembrolizumab arm: <21 months after the start of the model; nivolumab with chemotherapy arm:<8 months after the start of the model)

The company assumed that re-treatment with immunotherapies would be permitted if progression had occurred at least 6 months after the last dose of immunotherapy in the adjuvant or neoadjuvant setting; this assumption aligns with the NICE TA823[12] AC view, clinical advice[48] to the company and BlueTeq prescribing forms[49] for metastatic immunotherapy treatments.

The company used the following approach to determine the proportion of patients receiving each first-line treatment:

- in all treatment arms, 15% of patients were assumed to receive a targeted treatment for metastatic NSCLC positive for biomarkers (e.g., EGFR, KRAS G12C, ALK or ROS-1). As a simplifying assumption, all these patients were assumed to receive osimertinib (the treatment of choice for EGFR-positive disease [EGFR is the most common marker])
- patients who did not receive targeted treatment and were eligible for immunotherapy treatment, were split by PD-L1 status and squamous versus non-squamous histology (if PD-L1 TPS < 50%)
- patients who were not eligible for targeted or immunotherapy treatment were assumed to be treated with chemotherapy

The proportions of patients receiving each first-line treatment are presented in Table 23.

Table 23 First-line treatment market shares for metastatic NSCLC in company model

Treatment	Cohort description	Periadjuvant pembrolizumab or neoadjuvant nivolumab with chemotherapy		Neoadjuvant chemotherapy	Surgery alone
		IO-eligible	IO-ineligible	IO-eligible	IO-eligible
Osimertinib	Eligible for a TKI	15%	15%	15%	15%
Pembrolizumab + carboplatin+ paclitaxel	PD-L1 <50% and squamous	32.95%	0%	32.95%	33%
Pembrolizumab + pemetrexed+ PDC	PD-L1 <50% and non-squamous	23.66%	0%	23.66%	24%
Pembrolizumab	PD-L1 ≥50%	22.71%	0%	22.71%	23%
Atezolizumab	PD-L1 ≥50%	5.68%	0%	5.68%	6%
Carboplatin+ paclitaxel	Squamous	0%	49.47%	0.00%	0%
Pemetrexed+ PDC	Non-squamous	0%	35.53%	0.00%	0%

IO=immunotherapy; PDC=platinum doublet chemotherapy; PD-L1=programmed death-ligand 1; TKI=tyrosine kinase inhibitor
Source: CS, Table 45

Second-line treatments

Based on clinical advice,[48] the company assumed that, in the second-line metastatic treatment setting, irrespective of treatment arm or immunotherapy eligibility status, 40% of patients received best supportive care (BSC). The company also assumed that no patients would receive targeted treatments or immunotherapies as all eligible patients would have received these treatments in the first-line metastatic setting. For the 60% of patients remaining (i.e., those who do not receive BSC), the company assumed that half would be treated with docetaxel (30%) and the other half would be treated with platinum doublet chemotherapy (30%).

Estimating mean survival by first-line metastatic setting treatment

For each first-line metastatic NSCLC treatment option, the transition from the DM health state to the death health state (OS), and time to second line treatment (PFS), were modelled using exponential distributions. The distributions were chosen so that estimated median OS and median PFS matched the values reported in the pivotal trials for each treatment (Table 24). For pemetrexed+platinum (non-squamous histology) and carboplatin+paclitaxel (squamous histology), OS and PFS HRs versus the corresponding pembrolizumab reference treatment were obtained from the KEYNOTE-671 trial.

Table 24 Parameters used to model OS and PFS in the DM health state

Treatment regimen (metastatic setting)	Indicated population	Exponential weekly rate or HR* (SE)		Source
		OS	PFS	
Pembrolizumab+ pemetrexed+PDC	Non-squamous NSCLC	0.0073 (0.0004)	0.0176 (0.0011)	KEYNOTE-189[50] data on file (data cut-off: 08 Mar 2022)
Pembrolizumab+ carboplatin+paclitaxel	Squamous NSCLC	0.0093 (0.0008)	0.0198 (0.0017)	KEYNOTE-407[51] data on file (data cut-off: 23 Feb 2022)
Osimertinib	EGFR+ NSCLC (assumed efficacy for proportion on TKI)	0.0041 (0.0002)	0.0084 (0.0008)	Ramalingam[52] and Soria[53] FLAURA trial
Pembrolizumab	PD-L1 ≥ 50% NSCLC	0.0080 (0.0009)	0.0245 (0.0022)	KEYNOTE-042 data on file (data cut-off date: 28 May 2021)
Atezolizumab	PD-L1 ≥ 50% NSCLC	0.0079 (0.0009)	0.0197 (0.0023)	Herbst[54] IMpower110 trial
Pemetrexed+PDC	Non-squamous NSCLC	*1.67 (0.09)*	*2.00 (0.09)*	KEYNOTE-189[50] data on file (data cut-off: 08 Mar 2022)
Carboplatin+(nab-) paclitaxel	Squamous NSCLC	*1.41 (0.09)*	*1.61 (0.09)*	KEYNOTE-407[51] data on file (data cut-off: 23 Feb 2022)

* HRs indicated in italics and applied to corresponding rate for pembrolizumab arm of relevant trial
EGFR=epidermal growth factor receptor; HR=hazard ratio; NSCLC=non-small-cell lung cancer; OS=overall survival; PDC=platinum doublet chemotherapy; PFS=progression-free survival; SE=standard error; TKI=tyrosine kinase inhibitor
Source: CS, Table 46 and Table 47

The weekly DM health state OS hazard for each treatment arm was calculated as a weighted average of the expected mean OS associated with each first-line metastatic treatment and the

proportion of patients receiving that treatment. Expected PFS was similarly estimated based on the distributions of first-line treatments received and the ratio of mean PFS to mean OS (calculated via area under the exponential curves); this ratio was used to calculate overall DM health state utility values and weekly disease management costs.

The company explains that, since the metastatic NSCLC trials[50-54] used to inform efficacy of first-line treatments did not typically enrol previously resected patients, an adjustment factor (1.0604) was applied to the OS hazard rates to account for the slightly higher mortality of patients in the SEER Medicare database[55] who had DM NSCLC after prior resection (who reflect the KEYNOTE-671 cohort). The adjusted weekly rates of death in the DM health state for each treatment are presented in Table 25.

Table 25 Hazard of death in the DM health state by treatment arm

Model arm	Expected survival in DM health state, weeks			Exponential weekly rate of death in DM health state	
	OS	PFS	Ratio PFS:OS	Based on NSCLC trials[50-54]	After applying adjustment factor[†]
Periadjuvant pembrolizumab (IO-eligible)	140	60	0.43	0.0071	0.0076
Periadjuvant pembrolizumab (IO-ineligible)	104	43	0.42	0.0097	0.0102
Neoadjuvant chemotherapy	140	60	0.43	0.0071	0.0076
Neoadjuvant nivolumab with chemotherapy (IO-eligible)	140	60	0.43	0.0071	0.0076
Neoadjuvant nivolumab with chemotherapy (IO-ineligible)	104	43	0.42	0.0097	0.0102
Surgery alone	140	60	0.43	0.0071	0.0076

[†] Adjustment factor of 1.0604 calculated by dividing OS hazard rate in SEER[55] (0.00756) by OS hazard rate in model (0.00713, using metastatic NSCLC trials[50-54])
DM=distant metastases; IO=immunotherapy; OS=overall survival; PFS=progression-free survival
Source: CS, Table 48

4.9 Health-related quality of life

4.9.1 Health state utility values

HRQoL data were collected during the KEYNOTE-671 trial from patients using the EQ-5D-5L questionnaire. EQ-5D-5L data (IA2 data cut: 10th July 2023) were mapped to EQ-5D-3L (UK value set) using the algorithm developed by the Decision Support Unit[56] to generate health state utility values. As there was no clinically meaningful differences in HRQoL between the

treatment arms during either the neoadjuvant or adjuvant phases of the KEYNOTE-671 trial, utility data were pooled across treatment arms to estimate the average utility for all patients in the trial. The health state utility values derived from KEYNOTE-671 trial data and used in the company model are presented in

Table 26.

Table 26 Summary of utility values used in company model

Health state	Utility (mean)	SE†	Source
EF (without AEs)	0.882	0.008	Mapped EQ-5D-3L values from KEYNOTE-671 trial
LR/P	0.776	0.034	
DM (pre-progression)	0.727	0.038	
DM (post-progression)	0.657	0.030	KEYNOTE-407 TRIAL,[51] February 2022 % squamous, KEYNOTE-671: 43.2%
	0.679	0.026	KEYNOTE-189 trial,[50] March 2023 % non-squamous, KEYNOTE-671 trial: 56.8%
Grade ≥3 AEs	-0.091	0.016	KEYNOTE-671 trial

† SE from utility analysis doubled to account for repeated measures
AE=adverse event; EF=event-free; EQ-5D-3L=EuroQol-5 dimensions-3 levels; DM=distant metastases; LR/P=locoregional recurrence or progression; SE=standard error
Source: CS, Table 52

It was not possible to generate utility values for pre- versus post-progression in the DM health state as limited follow-up data were available from the KEYNOTE-671 trial. The company therefore assumed that the KEYNOTE-671 trial DM health state utility values represented utility in the pre-progression DM sub-state only. The post-progression DM utility value was estimated using EQ-5D data collected during recent RCTs exploring the effectiveness of pembrolizumab as a treatment option for patients with untreated NSCLC (KEYNOTE-189 trial[50] [non-squamous NSCLC] and KEYNOTE-407[51] trial [squamous NSCLC]) weighted by the proportion of patients with squamous or non-squamous histology in the KEYNOTE-671 trial.

Health state utility values were adjusted to account for the decrease in HRQoL that occurs with age using general population utility values estimated by Hernandez-Alava.[56] and the baseline age and sex values of patients in the KEYNOTE-671 trial (Table 19).

4.9.2 Adverse event utility decrements

The company model includes all-cause Grade ≥3 AEs that occurred with a frequency of ≥5% in either arm of the KEYNOTE-671 trial (ITT population) or in the neoadjuvant nivolumab with chemotherapy arm of the CheckMate-816 trial.[22] The CheckMate-816 trial[22] only captured AEs for 30 days after the last neoadjuvant dose and so did not record chemotherapy-related AEs for the 15% of patients who received adjuvant chemotherapy. To account for this, AE risks for

patients treated with nivolumab were estimated by multiplying the rate of each AE observed in the neoadjuvant arm of the KEYNOTE-671 trial by 0.15. AE rates in the surgery alone arm were conservatively assumed to be zero.

A disutility for all Grade ≥3 AEs was estimated from KEYNOTE-671 trial EQ-5D data (

Table 26).
The QALY loss associated with AEs was calculated for each treatment arm by multiplying the treatment-specific incidence rate for each AE by the disutility, mean duration (in weeks) per AE episode and mean number of episodes per patient in the KEYNOTE-671 trial (CS, Table 49). The total QALY loss associated with AEs was then applied as a one-off decrement in the first model cycle.

4.10 Resources and costs

4.10.1 Drug costs

Unit costs

Unit drug costs for pembrolizumab, chemotherapy, comparator regimens and subsequent treatments are presented in Table 27. Pembrolizumab, atezolizumab, nivolumab and osimertinib are available to the NHS at confidential discounted PAS prices.

Table 27 Unit drug costs for treatments included in company model

Regimen or component	Strength per vial or pack	Pack size	List price per vial or pack
Atezolizumab*	1,200mg	1	£3,807.69
Carboplatin	450mg	1	£14.69
Cisplatin	50mg	1	£5.58
Docetaxel	160mg	1	£16.04
Gemcitabine	200mg	1	£4.13
Nivolumab*	40mg	1	£439.00
Osimertinib*	80mg	30	£5,385
Paclitaxel	300mg	1	£17.40
Pembrolizumab*	100mg	1	£2,630.00
Pemetrexed	100mg	1	£71.43
Vinorelbine	50mg	10	£158.63

*Available to the NHS at a confidential discounted PAS price
Source: CS, Table 55

The company sourced drug administration costs for all treatment regimens from the NHS Cost Collection 2021/22[57]

Table 28).

Table 28 Drug administration costs used in company model

Regimen	Unit cost per administration	NHS Cost Collection 2021/2022[57] healthcare resource group code
Neoadjuvant/adjuvant setting		
Pembrolizumab (or nivolumab) in combination with chemotherapy (neoadjuvant phase)	£354	SB13Z: Deliver Complex Parenteral Chemotherapy at First Attendance
Pembrolizumab monotherapy (adjuvant phase)	£287	SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance
Neoadjuvant chemotherapy	£354	SB13Z: Deliver Complex Parenteral Chemotherapy at First Attendance
Distant metastases health state		
Immunotherapy monotherapy or single agent chemotherapy	£287	SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance
Combination chemotherapy (±pembrolizumab)	£354	SB13Z: Deliver Complex Parenteral Chemotherapy at First Attendance

Source: CS, Table 56

Time on treatment

Time on treatment (ToT) for each component of the periadjuvant pembrolizumab regimen was based on the observed proportions of patients who received each scheduled cycle in the KEYNOTE-671 trial (CS, Table 57). At the time of the data cutoff, no patients remained on neoadjuvant or adjuvant treatment and therefore the observed proportions of patients who received each treatment cycle could be used directly without the need to extrapolate trial ToT data. In the model, the costs of treatment were applied at fixed intervals of 3 weeks (Q3W), starting with the first neoadjuvant infusion at cycle 0. In the pembrolizumab arm, the first dose of adjuvant treatment was applied at Week 24 to account for the treatment-free period pre- and post-surgery observed in the KEYNOTE-671 trial (CS, Table 58).

Treatment duration for neoadjuvant nivolumab with chemotherapy was based on reported CheckMate-816 trial[22] data; a weekly exponential discontinuation rate was calculated (93.8% of patients completed three doses of Q3W neoadjuvant nivolumab with chemotherapy over a 6 week period).

4.10.2 Health state and resource use costs

Event-free, LR/P and DM health state disease management costs were applied in each model cycle (CS, Table 59 and Table 60). The company applied TA823[12] resource use estimates as these were preferred by company clinical experts.[48] Hospitalisations were not costed as part of TA823[12] so, based on clinical advice, the company assumed that hospitalisations occurred once every 2 years in the event-free health state and, for all other health states, used the TA761[7] hospitalisation rates. Although disease management costs varied by health state, the same total weekly health state cost was applied to all patients irrespective of treatment arm.

To estimate a single DM health state resource use estimate, TA823[12] (two DM health states) resource use estimates were weighted by the estimated time patients spend in the pre-progression and post-progression DM states, as determined by the modelled distribution of first-line market shares and the resulting ratio of PFS to OS (Table 24).

Event-free health state

One-off costs were applied in the event-free health state to account for the costs of initial surgery and adjuvant radiotherapy following surgery. Costs were calculated based on KEYNOTE 671 and CheckMate-816[22] trial observed proportions of patients who underwent surgery as planned and who received post-surgery radiotherapy (CS, Table 61). The timings of the costs were based on KEYNOTE 671 trial and CheckMate-816[22] trial mean times from final neoadjuvant dose to surgery and mean time from surgery to the initiation of adjuvant radiotherapy. The surgery and radiotherapy unit costs are presented in Table 29.

Table 29 Surgery and radiotherapy unit costs applied in company model

Resource	Unit cost	Notes and unit cost source
Surgery	£11,273	NHS Cost Collection 2021/22:[57] DZ02H-K, Complex Thoracic Procedures, 19 years and over, with CC Score 6+ CC Score 0 to 6+ (weighted average)
Radiotherapy	£5,557	NHS Cost Collection 2021/22,[57] replicating the costing approach used in NG122[10] (weighted average of continuous hyperfractionated accelerated radiotherapy, hyperfractionated accelerated radiotherapy, and standard fractionated radiotherapy)

Source: CS, Table 62

Local-regional recurrence or progression health state

In addition to the disease management costs applied per cycle, a one-off cost was included to account for the distribution of treatments that patients received for locally advanced disease; these were estimated based on clinical advice to the company[48] (

Table 30), which was that, in UK clinical practice, some patients receive durvalumab after chemoradiotherapy. Treatment with durvalumab was not included in the company model as the company considered that, as only a specific subset of patients (namely those with unresectable Stage III disease and PD-L1 ≥1%) are treated with durvalumab, the generalisability of pivotal trial results to a resected-and recurred-population is uncertain, and any effect would be complex to implement in a Markov cohort model. The company therefore assumed patients received the same treatments, regardless of prior treatment in the neoadjuvant/adjuvant setting.

Table 30 Treatment costs applied in LR/P health state

Resource element in LR/P state	% of patients[48]	Unit cost	Source
Salvage surgery	2%	£11,273	NHS Cost Collection 2021/22:[57] DZ02H-K, Complex Thoracic Procedures, 19 years and over, with CC Score 6+ CC Score 0 to 6+ (weighted average)[57]
Radiotherapy (CRT)	30%	£5,557	NHS Cost Collection 2021/22,[57] replicating the costing approach used in NG122[10] (weighted average of continuous hyperfractionated accelerated radiotherapy, hyperfractionated accelerated radiotherapy, and standard fractionated radiotherapy)
Radiotherapy (alone)	20%		
Systemic therapy (chemotherapy alone)	30%	£1,977	Costed as vinorelbine+cisplatin (5.3 weeks treatment in KEYNOTE-671 trial). This cost is also added as the chemotherapy component of CRT
BSC	18%	£0	Assumption

BSC=best supportive care; CC=complications; CRT=chemoradiotherapy; LR/P=local-regional recurrence or progression; NICE=National Institute for Health and Care Excellence; NG=NICE Guidance
Source: CS, Table 63

Distant metastases health state

Based on clinical advice,[48] the company applied a one-off cost to all patients who entered the DM state. This cost was for the appointments and scans (e.g., a positron emission tomography scan to assess the extent of disease) that a patient receives on diagnosis of distant metastasis.

As described in Section 4.8, drug acquisition and administration costs associated with first-line and second-line systemic treatments for metastatic NSCLC were included in the model. The dosing schedules and stopping rules for metastatic NSCLC treatments are presented in Table 64 of the CS. For simplicity, times on first-line treatments were assumed to be equal to the modelled exponential rate of PFS failure, subject to any specified maximum treatment duration. The mean time on treatment for second-line treatments (CS, Table 65) were estimated based on data from 9,121 patients (Flatiron database[58]). The cohort consisted of patients who were previously treated with first-line systemic anti-cancer therapy for advanced or metastatic NSCLC and who initiated second-line treatment.

4.10.3 Adverse event costs

Unit costs for Grade ≥3 AEs were sourced from the NHS Cost Collection 2021/22[57] (

Table 31). The total cost associated with AEs was calculated as the sum-product of AE incidence rates, mean number of episodes per patient with the AE and mean cost per episode of the AE (adjusting for proportions with and without hospitalisations). For AEs that did not result in hospitalisation, a unit cost of £160 was applied to represent the cost of a clinical

oncology outpatient attendance. The total AE cost was applied as a one-off cost at the start of the model.

Table 31 Unit cost per Grade ≥3 adverse events

Grade ≥3 AEs	Cost per event (with hospitalisation)	NHS Cost Collection 2021/22[57] health care resource group code
Anaemia	£941.32	SA03G, SA03H, SA04G, SA04H, SA04J, SA04K, SA04L, SA05G, SA05H, SA05J, SA08G, SA08H, SA08J (weighted average)
Neutropenia	£1,365.64	SA08G, SA08H, SA08J (weighted average)
Neutrophil count reduced	£1,365.64	Assumed same cost as neutropenia
Platelet count decreased	£993.35	SA12G, SA12H, SA12J, SA12K (weighted average of costs for thrombocytopenia)
White blood cell count decreased	£1,365.64	SA08G, SA08H, SA08J (weighted average)

AE=adverse event
Source: CS, Table 66

4.10.4 End of life costs

The company applied a one-time terminal care cost of £7,429 on entry into the death health state. This cost has been inflated to the current cost year from the original value of £6,207, which was sourced from the Georghiou and Bardsley[59] study.

4.11 Severity modifier

The company considered that periadjuvant pembrolizumab does not qualify for a severity modifier in this indication as the expected QALY loss for standard of care versus the general population does not meet any severity modifier threshold.

5 COST EFFECTIVENESS RESULTS

The cost effectiveness results presented in this section were generated by the company's clarification model (and therefore are not presented in the CS) which removed the discounts applied to comparator list prices and implemented minor amendments to model inputs (company response to clarification question B6, Table 8).

The company base case pairwise deterministic results are presented in Table 32. Company base case pairwise probabilistic results (1,000 model iterations) are presented in Table 33. Both sets of results were generated using the PAS price for pembrolizumab and list prices for all other drugs.

Table 32 Company base deterministic pairwise results (PAS price for pembrolizumab)

Treatment	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Periadjuvant pembrolizumab	[redacted]	[redacted]	-	-	-
Neoadjuvant chemotherapy	[redacted]	[redacted]	[redacted]	1.93	[redacted]
Neoadjuvant nivolumab with chemotherapy	[redacted]	[redacted]	[redacted]	0.91	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	2.66	[redacted]

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: Company clarification response Table 10

Table 33 Company base probabilistic pairwise results (1,000 iterations PAS price for pembrolizumab)

Treatment	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Periadjuvant pembrolizumab	[redacted]	[redacted]	-	-	-
Neoadjuvant chemotherapy	[redacted]	[redacted]	[redacted]	1.84	[redacted]
Neoadjuvant nivolumab with chemotherapy	[redacted]	[redacted]	[redacted]	0.86	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	2.66	[redacted]

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: company clarification response Table 11

5.1 Sensitivity analyses

The company varied parameter input values individually in deterministic sensitivity analyses. Upper and lower values were based on 95% CIs or by ±20% of the mean base case value. Cost effectiveness results for all comparisons were most sensitive to i) the exponential rate of distant metastases and death from the LR/P health state, ii) the exponential rate of OS and PFS failure with treatments for metastatic NSCLC, and iii) the utility value in the event-free health state.

5.2 Validation

To verify company model cost effectiveness results, quality control procedures were undertaken to ensure that i) the mathematical calculations were performed correctly and were

consistent with the model's specifications, and ii) that the parameter values in the model were correct.

The internal validity of the model was also assessed by comparing modelled efficacy outcomes against the original sources that informed the efficacy inputs. Specifically, the EFS curves predicted for the two arms of the KEYNOTE-671 trial were plotted alongside the observed EFS K-M curves to ensure that the curves were well-aligned during the trial period. Similarly, data from the SEER-Medicare KEYNOTE-671-matched cohort were used to validate model EFS and OS predictions for the neoadjuvant chemotherapy arm.

A total of 12 clinical experts treating NSCLC within the UK NHS were consulted across two advisory boards. Clinicians validated, and informed the derivation of, key model assumptions (including cure, subsequent treatments and resource use post-recurrence or progression).

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 Overview of modelling issues identified by the EAG

The company submitted an economic model, developed in Microsoft® Excel, to generate cost effectiveness results for the comparison of periadjuvant pembrolizumab versus comparators for adult patients with resectable Stage II, IIIA or IIIB (T3/4N2) NSCLC.

In response to clarification question B6, the company populated the model with comparator list prices; this had a substantial effect on the size of ICERs per QALY gained. During the process of updating the model with list prices, the company identified three minor errors:

- changed source of general population utility values from Ara & Brazier[60] to Hernandez-Alava[56]
- updated CT scan resource use estimates
- corrected the cost of radiotherapy

The impact of resolving these errors on cost effectiveness results was negligible.

The EAG is satisfied that the company clarification model algorithms are accurate and that the parameter values used in the model match the values presented in the CS (or clarification response) and the original sources.

A summary of the EAG's critique of the company model is presented in Table 34.

Table 34 Summary of the EAG critique of the company's cost effectiveness model

Aspect considered	EAG comment	Section of EAG report
Model structure	• The company model structure is appropriate.	NA
Population	• Clinical advice to the EAG is that the KEYNOTE-671 trial population is younger than the NHS population who, if periadjuvant pembrolizumab were recommended by NICE, would be eligible for treatment with periadjuvant pembrolizumab; clinical advice to the EAG is that older, less fit patients may not be suitable for treatment with chemotherapy.	6.2
Comparators	• The company only provided clinical effectiveness results for the comparison of periadjuvant pembrolizumab versus three comparators listed in the final scope issued by NICE (neoadjuvant nivolumab with chemotherapy, neoadjuvant chemotherapy and surgery alone).	6.3
Event-free survival health state transition probabilities	• The EAG has concerns about the process used by the company to select combinations of distributions to estimate transitions out of the event-free health state. However, due to mature KEYNOTE-671 trial EFS data (median follow-up 62 months) and the assumption that the probability of transitioning out of the event-free health state is zero after 5 years, choosing alternative distributions only has a small impact on cost effectiveness results.	6.4

Aspect considered	EAG comment	Section of EAG report
Use of company EFS NMA results	• In the company base case, time-varying HR (fixed-effects) EFS NMA results were applied to the periadjuvant pembrolizumab data to generate EFS estimates for patients treated with neoadjuvant nivolumab with chemotherapy and those treated with surgery alone; HRs were kept constant beyond the observed KEYNOTE-671 trial follow-up period. **EAG scenarios**: (i) Use time-varying HRs but apply a HR of 1 to the pembrolizumab EFS curve after a given time period for each trial and (ii) use constant HRs (fixed-effects) NMA results to estimate EFS for patients treated with neoadjuvant nivolumab with chemotherapy and patients treated with surgery alone. • There is no statistically significant difference in EFS for periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy in any of the company NMA results. **EAG scenario**: conduct an exploratory scenario assuming EFS is the same for patients treated with periadjuvant pembrolizumab and patients treated with neoadjuvant nivolumab with chemotherapy.	0
Local-regional recurrence/ progression	• The company estimated transition probabilities from the model LR/P health state using data from 43 SEER-Medicare study[55] patients. The exclusion of patients who received chemotherapy alone, and the relatively high proportion ([redacted]%) who underwent surgery, are not in line with the proportions of patients who received LR/P treatments in the company model (based on clinician estimates). The company's approach may produce optimistic (long) time to progression estimates. Using more pessimistic progression rates has a minimal impact on cost effectiveness results and therefore the EAG has not provided cost effectiveness results generated using alternative rates.	NA
Distant metastases	• The data sources used by the company to estimate transition probabilities are appropriate and the treatments included in the model align with the NHS treatment pathway. • The modelled mean survival of patients with metastatic disease who are treated with immunotherapies is consistent with the life year gains modelled in previous NICE appraisals.[61,62]	NA
Mortality rates for patients who remain in the event-free health state for ≥5 years	• The specific cure assumptions used in the company model were sourced from TA876[11] but remain uncertain. However, results from company scenario analyses exploring the impact of more pessimistic and optimistic cure assumptions showed that changing these assumptions had limited impact on cost effectiveness results. • Evidence from the literature[63,64] suggests that patients alive after 5 years may experience long-term excess mortality due to the increased risk of a second cancer diagnosis. **EAG scenario**: based on data reported in the literature[63,64], adjust the mortality rate for patients assumed to be cured after 5 years so that it is higher than the general population mortality rate.	6.6
Utility values	• The event-free health state utility value (sourced from the KEYNOTE-671 trial and adjusted to exclude the effect of AEs) is higher than the age- and sex-matched general population utility value. **EAG scenario**: use the age- and sex-matched general population utility value to represent HRQoL in the event-free health state.	6.7
Treatment costs	• Treatment costs were estimated appropriately and supported by clinical advice.	NA
Healthcare resource use	• The company's resource use estimates are supported by clinical advice.	NA
Adverse events	• The modelling of AEs is appropriate.	NA

Aspect considered	EAG comment	Section of EAG report
Half-cycle correction	• The company model cycle length is 1 week. A half-cycle correction was applied to costs and health outcomes to account for mid-cycle progressions. The EAG considers that the application of a half-cycle correction is not necessary when the cycle length is only 1 week. No change made to the company model.	NA
PSA	• The PSA was appropriately specified and correctly implemented.	NA

AE=adverse event; EAG=External Assessment Group; NMA=network meta-analysis; PSA=probabilistic sensitivity analysis

6.2 Generalisability of KEYNOTE-671 trial results to NHS patients

Clinical advice to the company was that treatment would likely be stopped for patients who achieve pCR after surgery. Therefore, the relevance of the KEYNOTE-671 trial results to NHS patients is uncertain. In addition, it is unclear how clinicians will determine which patients are likely to benefit most from post-surgery immunotherapy. Further, clinical advice to the EAG is that KEYNOTE-671 trial patients are considerably younger (mean=63.1 years) than NHS patients (average age of 70 years) and that older, less fit NHS patients may not be suitable for treatment with immunotherapy treatment.

The company has carried out three scenario analyses that removed the cost of pembrolizumab in the adjuvant setting for patients achieving a pCR (CS, Table 11, scenarios 24, 25 and 26). The EAG considers that removing the costs of adjuvant pembrolizumab treatment without any corresponding adjustment to effectiveness data will slightly overestimate the clinical and cost effectiveness of periadjuvant pembrolizumab. Further, clinical advice[65] to the company is that whilst adjuvant treatment would likely be stopped for patients who achieve a pCR after surgery, pCR status is not currently used in clinical decision-making. The EAG therefore considers that results from these scenarios are currently of limited value for decision-making.

The EAG highlights that in the KEYNOTE-671 trial periadjuvant pembrolizumab arm, [redacted]/396 ([redacted]%) patients discontinued adjuvant pembrolizumab treatment (Table 35). The EAG has concerns that not all patients completed adjuvant pembrolizumab treatment and therefore the tolerability, treatment cost and benefit of periadjuvant pembrolizumab in an NHS population is uncertain.

Table 35 Reasons for discontinuing pembrolizumab in the adjuvant setting (KEYNOTE-671 trial data)

Reason for discontinuation	n (%)
Adverse event	[redacted]
Progressive disease	[redacted]
Clinical progression	[redacted]
Physician decision	[redacted]
Withdrawal of consent	[redacted]

Source: MSD data on file[48]

6.3 Comparator treatments

In the CS, the company provided cost effectiveness evidence for the comparison of periadjuvant pembrolizumab versus neoadjuvant chemotherapy (listed in the final scope issued by NICE as platinum based chemotherapy), neoadjuvant nivolumab with chemotherapy and surgery alone. At clarification, NICE asked the company to provide cost effectiveness evidence for the comparison of periadjuvant pembrolizumab versus periadjuvant durvalumab and versus adjuvant osimertinib. The company provided a detailed response explaining why they considered that providing cost effectiveness evidence for these two comparators was not appropriate. The company also suggested ways that, if these drugs were recommended prior to the NICE AC meeting for periadjuvant pembrolizumab, evidence could be incorporated into the NICE decision-making process at this later date.

Clinical advice to the EAG is that for patients who are suitable for neoadjuvant chemotherapy, neoadjuvant nivolumab with chemotherapy is the preferred treatment regimen and that very few patients in NHS clinical practice currently receive neoadjuvant chemotherapy. The EAG therefore considers that neoadjuvant chemotherapy is not a relevant comparator. However, for completeness, EAG cost effectiveness results for the comparison of periadjuvant pembrolizumab versus neoadjuvant chemotherapy are presented in Appendix 8.3 (Table 46 and Table 47).

Clinical advice to the EAG is that patients who are suitable for surgery alone will have a lower risk of recurrence than those who are at higher risk of recurrence and would be offered systemic treatment. The EAG, therefore considers that surgery alone is a less relevant comparator than neoadjuvant nivolumab with chemotherapy.

6.4 Generating intervention effectiveness estimates

In the company model, at each cycle, patients in the event-free health state can stay in that health state or move to any of the other three health states (local-regional recurrence or progression, distant metastases or death).

When choosing which distributions to use to generate transition probabilities out of the event-free state for patients treated with periadjuvant pembrolizumab and neoadjuvant chemotherapy, the company considered a total of 397 different parametric distribution combinations to generate probabilities for moving out of the event-free health state. The company used a stepwise approach to select the base case parametric distributions. The process used is described in the CS (CS, pp11-112) and summarised in Section 4.2.

When patients are at risk of experiencing several events, there are challenges associated with model selection. Using the standard measure of statistical fit (i.e., Akaike Information Criterion) is not informative when assessing cause-specific hazards. Further, in contrast to the standard model selection procedure outlined in NICE TSD 14[66] for partitioned survival models, there is no standardised approach to distribution selection when estimating transition probabilities in multi-state models. Williams[46] relied on visual assessment of fit to the observed data, and an informal judgement of whether extrapolations were clinically plausible; the company followed this approach.

The EAG has the following concerns about the methods used by the company to assess model fit:

- whilst MSE results can quantify predictive accuracy (internal validity), the extent to which differences in MSE between combinations of parametric distributions used to model transitions between health states is sufficient to prefer or reject one combination over another is unclear
- the company approach involved using the same distribution combination for periadjuvant pembrolizumab and neoadjuvant chemotherapy; it is not clear how to evaluate a combination that provides a good fit (low MSE) to data from one arm but provides a poor fit (high MSE) to data from the other arm

Further, it is not clear how the company used visual inspection to exclude 49 combinations as there appear to be no substantial differences in visual fit to observed distributions, even after reducing the set of distribution combinations to n=67 (CS, Appendix M, Figures 17-19). The EAG considers that excluding distribution combinations based on MSE statistics and visual inspection is arbitrary and subjective; it is not clear whether alternative combinations of parametric distributions would generate EFS estimates that are as clinically plausible as company base case estimates.

To explore the impact on cost effectiveness results of choosing alternative distribution combinations, the EAG reviewed company scenario analysis results (CS, Table 73, scenarios 1 to 5). Results from these analyses demonstrate that choosing alternative distribution combinations generate very similar cost effectiveness results and therefore, based on

available data, the choice of distribution combination is not a key driver of cost effectiveness. The EAG considers that the lack of impact of different distribution combinations is due to:

- KEYNOTE-671 trial EFS data maximum follow-up being 62 months (5.2 years)
- in the model, for 95% of patients who remain event-free at 5 years, by year 7 the probability of disease progression is zero and the probability of death is the same as that for the age- and sex-matched general population.

6.5 Generating comparator EFS estimates

The company base case model is structured so that periadjuvant pembrolizumab provides no additional treatment benefit to patients after they have experienced recurrence (LR/P or DM). In the LR/P health state, the distribution and duration of treatment, the risk of further progression and the risk of death do not differ by prior treatment. In the DM health state, the distribution of treatments and expected survival vary only by the proportions of patients receiving each treatment who are eligible for immunotherapy. The incremental benefit of periadjuvant pembrolizumab versus comparator treatments therefore depends only on differences in the probability of remaining event-free over time, which determines the proportion of patients cured and the proportion of patients who experience recurrence.

The EAG considers that use of time-varying EFS HRs to compare the effectiveness of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy was not sufficiently justified by the company (see Section 3.7.7). Further, the EAG does not consider that it is appropriate to infer statistical significance (or lack of statistical significance) from time-varying HR NMA 95% CrIs and, therefore, that time-varying HR models do not provide robust statistical evidence to support a hypothesis that the EFS HRs change over time.

In the company base case, time-varying HRs were applied for the first 62 months (corresponding to the maximum KEYNOTE-671 trial EFS follow-up), with the last estimated HR applied for the remaining model time horizon (31.7 years). For example, the company time-varying HR EFS NMA results (fixed-effects model) suggest that the treatment effect for the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy are more favourable towards the end of the trial follow-up period (HRs at 6 and 48 months are 0.97 and 0.61 respectively). The EAG considers that treatment effect estimates at the end of the follow-up period are associated with greater uncertainty than earlier estimates as, over time, fewer patients provide data; this is not reflected in the size of the CrIs. The EAG considers that applying the last estimated HR over the remaining model time horizon may overestimate the incremental benefit of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy.

EAG revisions

There is no evidence to support periadjuvant pembrolizumab having a sustained treatment effect on EFS beyond the KEYNOTE-671 trial follow-up period. The EAG therefore considers that, rather than using the last time-varying EFS HR estimate for the remaining time horizon, it is more appropriate to apply an EFS HR of 1 to the pembrolizumab EFS curve for the time period that HRs have not been generated. The maximum follow-up for the CheckMate-816[67] trial data used in the company EFS NMA was not reported. Therefore, to estimate the effectiveness of neoadjuvant nivolumab with chemotherapy, the EAG has applied an EFS HR of 1 after 41.4 months (CheckMate-816[67] trial median follow-up [3 year data]) to periadjuvant pembrolizumab EFS estimates.

The study reporting surgery alone results that had the longest follow-up period was by Pisters[20] (EFS median follow-up of 64 months). The length of this median follow-up exceeded the KEYNOTE-671 trial median follow-up (29.8 months [ITT population]). The EAG has applied an EFS HR of 1 after 62 months (KEYNOTE-671 trial maximum EFS follow-up) to estimate EFS for patients treated with surgery alone.

The EAG considers that company time-constant HR (fixed-effects model) EFS NMA results should be used to generate EFS estimates for patients treated with neoadjuvant nivolumab with chemotherapy or surgery alone. The EAG has therefore carried out a revision that generates cost effectiveness estimates using time-constant HR (fixed-effects) EFS NMA results.

EAG exploratory scenario analyses

Company time-constant and time-varying (fixed-effects and random-effects) HR EFS NMA results show that there is insufficient evidence to conclude that periadjuvant pembrolizumab confers a statistically significant clinical benefit compared with neoadjuvant nivolumab with chemotherapy. The EAG has therefore carried out an exploratory analysis to assess the impact on model cost effectiveness results of assuming EFS is the same for patients treated with periadjuvant pembrolizumab and patients treated with neoadjuvant nivolumab with chemotherapy.

Company time-constant (fixed- and random-effects) and time-varying fixed-effects HR EFS NMA results show that periadjuvant pembrolizumab confers a statistically significant clinical benefit compared with surgery alone. The EAG has generated cost effectiveness results for the comparison of periadjuvant pembrolizumab versus surgery alone using company time-constant HR (fixed-effects model) EFS NMA results.

6.6 Mortality rates for patients remaining in the event-free health state for ≥5 years

In the company model, for 95% of patients who remain event-free at 5 years, the probability of progression to the LR/P or DM health states is set equal to zero by year 7 and the probability of death is set equal to general population mortality. Between 5 years and the end of 7 years, the cure proportion increases from 0% to 95% to prevent a visible kink in the EFS curve. Clinical advice to the EAG agrees with clinical advice to the company that the risk of recurrence is very low for patients who are event-free for ≥5 years and NSCLC diagnosed after 5 years is likely to be treated as a new primary cancer. Evidence from the literature[64] suggests that, after 5 years, mortality may remain higher than background mortality. A study[64] of patients with NSCLC in the Netherlands estimated the conditional relative 5-year survival for patients aged 60 to 74 years diagnosed with Stage III disease as 58% (i.e., for patients alive at 5 years, the probability of surviving an additional 5 years was 58% relative to the probability for an age- and sex-matched general population cohort), suggesting significant long-term excess mortality. In the Fink Neuboeck[63] study, the risk of developing a second primary tumour, particularly a second NSCLC, persisted for at least 10 years after surgery, although there was no negative impact on survival as most patients received curative treatment. The EAG therefore considers that whether, and the extent to which, mortality for patients in the event-free health state after 5 years should approximate general population mortality depends on duration of model follow-up, early diagnosis and treatment with curative intent.

EAG revision

The EAG has investigated the impact on cost effectiveness results of applying a more pessimistic mortality rate to patients assumed to be cured after 5 years. The EAG weighted the conditional 5-year relative survival rates reported in the Janssen-Heijnen study[64] by the (assumed) proportions of patients in each age and disease stage group from the KEYNOTE-671 trial. As baseline KEYNOTE-671 trial patient characteristics were not reported by both age and disease stage and KEYNOTE-671 age groups do not align with Janssen-Heijnen[64] study age groups, the EAG has assumed, irrespective of disease stage, that half of KEYNOTE-671 trial patients are in the 45-59 years age group (54.6% of patients in the KEYNOTE-671 trial were <65 years of age). A conditional relative survival rate of 95% is considered to reflect minimal excess mortality;[68] this was divided by the weighted conditional 5-year relative survival rate (65.4%) to estimate the relative increase in mortality risk (1.453). The EAG applied this risk factor to company model age- and sex-matched general population mortality rates to patients who remained in the event-free health state for ≥5 years.

Table 36 Parameters used to estimate relative increase in mortality for patients assumed to be cured after 5 years

Disease stage	Age group	Conditional 5-year relative survival at 5 years	Assumed proportions KEYNOTE-671 trial*	Weighted conditional 5-year relative survival rate
II	45-59 ye8.2ars	78%	14.85%	65.4%
	60-74 years	64%	14.85%	
III	45-59 years	68%	35.15%	
	60-74 years	58%	35.15%	

*The proportion of patients in each disease stage group were assumed to be equally split between the two age groups
Sources: Janssen-Heijnen[64] and CS, Table 10

6.7 Utility values

The company used a utility value of 0.882 to reflect patient HRQoL in the event-free health state. This value was generated from KEYNOTE-671 trial data (EQ-5D-5L data mapped to EQ-5D-3L data using the Hernandez-Alava algorithm[56]) which were adjusted to exclude the effect of AEs. The effect of AEs on HRQoL was modelled using a one off disutility applied during the first model cycle.

The event-free health state utility value of 0.882 is higher than the utility value for an age- and sex-matched general population cohort.[60] The EAG has explored the impact on cost effectiveness results of using the lower age- and sex-matched general population utility value (0.822) to represent HRQoL in the event-free health state.

6.8 Impact of EAG revisions on company base case cost effectiveness results

The EAG has made the following revisions to the company base case cost effectiveness analysis:

- HR of 1 applied to pembrolizumab EFS curve after 41.4 months and 62 months for comparisons versus neoadjuvant nivolumab with chemotherapy and versus surgery alone respectively (R1)
- time constant HRs (fixed-effects model) used to model EFS for patients treated with neoadjuvant nivolumab with chemotherapy or surgery alone (R2)
- risk factor applied to general population mortality rates for patients assumed to be cured after 5 years (R3)

The EAG has carried out exploratory analyses to assess the impact on model outcomes of the following:

- no difference in EFS between periadjuvant pembrolizumab and neoadjuvant nivolumab with chemotherapy (C1)
- age- and sex-matched general population utility value used to represent HRQoL in the event-free health state (C2)

Details of EAG revisions to the company model are presented in Appendix 8.2 of this EAG report. Deterministic pairwise cost effectiveness results for the comparison of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy and versus surgery alone are provided in Table 38 and Table 40 respectively.

Deterministic pairwise cost effectiveness results for the comparison of periadjuvant pembrolizumab versus neoadjuvant chemotherapy are presented in Appendix 8.3 (Table 46 and Table 47).

Probabilistic pairwise cost effectiveness results are presented in Table 39 and Table 41 and fully incremental analyses of probabilistic cost effectiveness results for the company base case and the EAG preferred scenario are presented in Table 42 and Table 43 respectively.

All results presented in this report have been generated using list prices except for pembrolizumab (PAS price). Cost effectiveness results, generated using available confidential drug prices (Table 37), are available in a confidential appendix.

Table 37 Pricing sources used in confidential appendix

Treatment	Price source/type of commercial arrangement
Pembrolizumab	Simple PAS discount
Nivolumab	Simple PAS discount
Atezolizumab	Simple PAS discount
Osimertinib	Simple PAS discount
Pemetrexed	CMU price
Carboplatin	eMIT price
Cisplatin	eMIT price
Docetaxel	eMIT price
Gemcitabine	eMIT price
Paclitaxel	eMIT price
Vinorelbine	eMIT price

CMU=Commerical Medicines Unit; eMIT=electronic Market Information Tool; PAS=Patient Access Scheme

Table 38 Deterministic pairwise results (periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy), PAS price for pembrolizumab and list prices for all other treatments

Scenario/EAG revisions	Periadjuvant pembrolizumab		Neoadjuvant nivolumab with chemotherapy		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.906**	[redacted]	-
R1) HR of 1 applied to pembrolizumab EFS curve after 41.4 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.537	[redacted]	[redacted]
R2) Time-constant EFS HR (fixed-effects model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.492	[redacted]	[redacted]
R3) Risk factor applied to general population mortality rates for patients assumed to be cured after 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.795	[redacted]	[redacted]
B. EAG preferred scenario (R1-R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.360**	[redacted]	[redacted]
C. EAG exploratory scenarios								
C1. No difference in EFS between periadjuvant pembrolizumab and neoadjuvant nivolumab with chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.052	[redacted]	-
C2. Age- and sex-matched general population utility value used to represent HRQoL in the event-free health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.872	[redacted]	[redacted]
C3. C1, C2 & R3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**-0.053**	[redacted]	-
C4. B & C2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.340**	[redacted]	[redacted]

EAG=External Assessment Group; EFS=event-free survival; HR=hazard ratio; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 39 Probabilistic pairwise results (periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy), PAS price for pembrolizumab and list prices for all other treatments

Scenario/EAG revisions	Periadjuvant pembrolizumab		Neoadjuvant nivolumab with chemotherapy		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.864**	[redacted]	**-**
B. EAG preferred scenario (R1-R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.364**	[redacted]	[redacted]
C. EAG exploratory scenarios								
C3. C1, C2 & R3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**-0.049**	[redacted]	**-**
C4. B & C2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.333**	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 40 Deterministic pairwise results (periadjuvant pembrolizumab versus surgery alone), PAS price for pembrolizumab and list prices for all other treatments

Scenario/EAG revisions	Periadjuvant pembrolizumab		Surgery alone		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2.662**	[redacted]	-
R1) HR of 1 applied to pembrolizumab EFS curve after 62 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.580	[redacted]	[redacted]
R2) Time-constant EFS HR (fixed-effects model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.431	[redacted]	[redacted]
R3) Risk factor applied to general population mortality rates for patients assumed to be cured after 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.417	[redacted]	[redacted]
B. EAG preferred scenario (R1-R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2.143**	[redacted]	[redacted]
C. EAG exploratory scenarios								
C1. Age- and sex-matched general population utility value used to represent HRQoL in the event-free health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2.551**	[redacted]	[redacted]
C2. B & C1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2.039**	[redacted]	[redacted]

EAG=External Assessment Group; EFS=event-free survival; HR=hazard ratio; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 41 Probabilistic pairwise results (periadjuvant pembrolizumab versus surgery alone), PAS price for pembrolizumab and list prices for all other treatments

Scenario/EAG revisions	Periadjuvant pembrolizumab		Surgery alone		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2.664**	[redacted]	-
B. EAG preferred scenario (R1-R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**2.109**	[redacted]	[redacted]
C2. EAG exploratory scenario (B & C1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.966**	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 42 Company clarification base case probabilistic results (fully incremental analysis), PAS price for pembrolizumab and list prices for all other treatments

Treatment	Cost	QALYs	ICER (£/QALY)
Surgery alone	[redacted]	[redacted]	-
Neoadjuvant nivolumab with chemotherapy	[redacted]	[redacted]	[redacted]
Periadjuvant pembrolizumab	[redacted]	[redacted]	[redacted]
Neoadjuvant chemotherapy	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 43 EAG preferred scenario probabilistic results (fully incremental analysis), PAS price for pembrolizumab and list prices for all other treatments

Treatment	Cost	QALYs	ICER (£/QALY)
Neoadjuvant nivolumab with chemotherapy	[redacted]	[redacted]	-
Surgery alone	[redacted]	[redacted]	[redacted]
Periadjuvant pembrolizumab	[redacted]	[redacted]	[redacted]
Neoadjuvant chemotherapy	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

6.9 Cost effectiveness conclusions

The EAG considers that there is substantial uncertainty around the comparative clinical effectiveness of periadjuvant pembrolizumab versus comparators. Cost effectiveness results rely on NMA HR results generated for a single outcome and the validity of assumptions around long-term effectiveness.

Neoadjuvant nivolumab with chemotherapy

The EAG revisions that had the biggest impact on cost effectiveness results were the use of time-constant EFS HRs (fixed-effects models) and applying a HR of 1 to the pembrolizumab EFS curve after 41.4 months. In the EAG exploratory scenario that assumed no difference in EFS, periadjuvant pembrolizumab was dominated by neoadjuvant nivolumab with chemotherapy.

Surgery alone

For the comparison of periadjuvant pembrolizumab versus surgery alone, EAG revisions had a limited impact on company cost effectiveness results.

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8 APPENDICES

8.1 Appendix 1 NMA results periadjuvant pembrolizumab versus neoadjuvant chemotherapy

Table 44 Time-constant HR EFS NMA results: periadjuvant pembrolizumab versus neoadjuvant chemotherapy

Analysis	HR (95% CrI)
Fixed effects	0.59 (0.48 to 0.72)

CrI=credible interval; EFS=event-free survival; HR=hazard ratio; NMA=network meta-analysis
Source: Extracted from CS, Table 27

Table 45 Summary of results from NMA with time-varying HR of treatments for the outcome of EFS of periadjuvant pembrolizumab versus relevant comparators

Comparator	Time-varying HR (95% CrI)											
	Time (months)											
	3	6	9	12	18	24	30	36	42	48	54	60
Neoadjuvant chemotherapy (fixed effects)	**0.72 (0.52 to 0.97)**	**0.62 (0.50 to 0.75)**	**0.58 (0.47 to 0.70)**	**0.55 (0.45 to 0.68)**	**0.53 (0.42 to 0.66)**	**0.51 (0.40 to 0.66)**	**0.50 (0.38 to 0.66)**	**0.50 (0.37 to 0.66)**	**0.49 (0.36 to 0.66)**	**0.49 (0.36 to 0.66)**	**0.48 (0.35 to 0.66)**	**0.48 (0.35 to 0.66)**
Neoadjuvant chemotherapy (random effects)	0.70 (0.27 to 1.76)	0.61 (0.23 to 1.49)	0.57 (0.22 to 1.39)	0.55 (0.21 to 1.34)	0.53 (0.20 to 1.29)	0.51 (0.19 to 1.26)	0.51 (0.19 to 1.23)	0.50 (0.19 to 1.22)	0.49 (0.18 to 1.21)	0.49 (0.18 to 1.20)	0.49 (0.18 to 1.20)	0.48 (0.18 to 1.19)

Hazard ratios (HR) represent the effect estimate for periadjuvant pembrolizumab versus the comparator (i.e., HR <1 favours periadjuvant pembrolizumab, HR >1 favours comparator). Cells shaded in grey indicate estimates based on model extrapolations. All **bolded** values are statistically significant at the 0.05 significance level.
CRI=credible interval; HR=hazard ratio
Source: Extracted from CS, Table 25 and Table 26

8.2 Appendix 2: EAG revisions to the company model

This appendix contains details of the changes that the EAG made to the company model.

EAG revisions	Implementation instructions
R1) EFS HR of 1 applied to pembrolizumab EFS curve after 41.4 months versus neoadjuvant nivolumab with chemotherapy and after 62 months versus surgery alone	**Insert sheet named 'EAG Revisions'** In cell C3 enter text "R1" Set value in cell D3 =1 In Sheet 'Specifications' Set value in cell G127 =IF('EAG Revisions'!$D$3=1,41.4/12,36.9) Set value in cell G128 =IF('EAG Revisions'!D$3=1,41.4/12,36.9) Set value in H127 =IF('EAG Revisions'!$D$3=1,62/12,36.9) Set value in H128 =IF('EAG Revisions'!$D$3=1,62/12,36.9) In Sheet 'Comparator HRs' Set value in cell N20 "Neoadjuvant nivolumab Set value in cell O20 "Periadjuvant pembrolizumab" Set value in cell P20 "Surgery alone" Set value in cell O21 =INDEX(Specifications!$H$127:$H$127,MATCH(subgroup_select,Specifications!$G$126:$G$126,0)) Set value in cell P21 =INDEX(Specifications!$H$128:$H$128,MATCH(subgroup_select,Specifications!$G$126:$G$126,0)) Set value in cell O22 =IF($D22<ROUND($O$21*years_to_weeks,0),0,IF($O$21=$P$21,1,MIN(1,($D22-ROUND($O$21*years_to_weeks,0))/ROUND(($P$21-$O$21)*years_to_weeks,0)))) Copy formula in cell O22 to range O22:O2631 Set value in cell P22 =1-O22 Copy formula in cell P22 to range P22:P2631 Set value in cell J22 =1*IF('EAG Revisions'!$D$3=1,$O22,$M22)+F22*IF('EAG Revisions'!$D$3=1,$P22,$N22) Copy formula in cell J22 to range J22:J2631
R2) Time-constant HRs (fixed-effects model) used to model EFS for neoadjuvant nivolumab with chemotherapy and surgery alone	In Sheet 'EAG Revisions' In cell C4 enter text "R2" Set value in cell D4 =1 In Sheet 'Specifications' Set value in cell G112 =IF(OR('EAG Revisions'!D$4=1,'EAG Revisions'!D$6=1),"Time-constant HR","Time-varying HR") Set value in cell G113 ==IF(OR('EAG Revisions'!D$4=1,'EAG Revisions'!D$6=1),"Time-constant HR","Time-varying HR")

R3) Risk factor applied to general population mortality rates for patients assumed to be cured after 5 years	In Sheet 'EAG Revisions' In cell C5 enter text "R3" Set value in cell D5 =1 In Sheet 'Life Tables' Set value in cell S10 = "Conditional 5 year survival rate at 5 years –" Set value in cell T10 = "Assumed proportions KEYNOTE-671 trial" Set value in cell S11 = 78 Set value in cell S12 = 64 Set value in cell S13 = 68 Set value in cell S14 = 58 Set value in cell T11 = 14.85% Set value in cell T12 = 14.85% Set value in cell T13 = 35.15% Set value in cell T14 = 35.15% Set value in cell T16 =SUMPRODUCT(S11:S14,T11:T14) Set value in cell T17 =95/T16 In Sheet 'Mortality by Cycle' Set value in cell I8 =@INDEX('Life Tables'!$N$21:$N$120,'Mortality by Cycle'!F7+1)*IF(AND(F7>=cure_EFS_startyr,'EAG Revisions'!$D$5=1),'Life Tables'!$T$17,1) Copy formula in cell I8 to range I8:I2617
C1) No difference in EFS between periadjuvant pembrolizumab and neoadjuvant nivolumab with chemotherapy* *R2 must be set =1 for revision	In Sheet 'EAG Revisions' In cell C6 enter text "R4" Set value in cell D6 =1 In Sheet 'Raw – Comparator HRs' Set value in cell T6 =IF('EAG Revisions'!D6=1,1,1.15) Set value in cell U6 =IF('EAG Revisions'!D6=1,0.2,-(LN(0.79)-LN(1.69))/(2*1.96))
C2) Age and sex-matched general population utility used to represent HRQoL in EF health state	In Sheet 'EAG Revisions' In cell C7 enter text "R5" Set value in cell D7 =1 In Sheet 'Utility' Set value in cell J121 =H121*(1-'Life Tables'!L21)+I121*'Life Tables'!L21

	Copy formula in cell J121 to range J121:J158 Set value in cell I29 =INDEX(F74:J158,MATCH('Mortality by Cycle'!O3,utilbyage_rowid,0),5) Set value in cell J29 =I29*0.2 In Sheet '<Central Data Control>' Set value in cell G186 =IF('EAG Revisions'!D7=1,3,2) In Sheet 'Mortality by Cycle' Set value in cell L7 =IF('EAG Revisions'!D$7=1,0,IF(agedisutil_source_select=1,$J7,$K7)) Copy formula in cell L7 to range L7:L2617

8.3 Appendix 3 Cost effectiveness results: periadjuvant pembrolizumab versus neoadjuvant chemotherapy

Table 46 Deterministic pairwise results (periadjuvant pembrolizumab versus neoadjuvant chemotherapy), PAS price for pembrolizumab and list prices for comparators/subsequent treatments

Scenario/EAG revisions	Periadjuvant pembrolizumab		Neoadjuvant chemotherapy		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.933**	[redacted]	**-**
B. EAG preferred scenario (R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.727**	[redacted]	**-**
C. EAG exploratory scenario								
C1. Age- and sex-matched general population utility value used to represent HRQoL in the event-free health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.845	[redacted]	**-**
C2. C1 & R3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.634**	[redacted]	**-**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Table 47 Probabilistic pairwise results (periadjuvant pembrolizumab versus neoadjuvant chemotherapy), PAS price for pembrolizumab and list prices for comparators/subsequent treatments

Scenario/EAG revisions	Periadjuvant pembrolizumab		Neoadjuvant chemotherapy		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A. Company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.837**	[redacted]	**-**
B. EAG preferred scenario (R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.639**	[redacted]	**-**
C2. EAG exploratory scenario (C1 & R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1.516**	[redacted]	**-**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

Single Technology Appraisal

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID5094]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

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

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 18 June 2024** using the below comments table.

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

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Time-varying HR NMA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"…the biological plausibility of time-varying HRs is unknown" (p13) "Clinical advice to the EAG is that, for the treatment comparisons included in the company's network of evidence, the biological plausibility of time-constant HRs and time-varying HRs is unknown." (p52)	"…the **long-term** biological plausibility of time-varying HRs is **uncertain**" "Clinical advice to the EAG is that, while the biological plausibility of a time varying treatment effect is obvious, its existence, magnitude and duration are associated with uncertainty, given the available data."	The company is concerned that this statement, as written, does not appear to reflect appropriate clinical advice. It is obvious that a time varying treatment effect is biologically *plausible*. The issue is that, given the trial designs available, its existence, magnitude and duration are associated with uncertainty and MSD consider that this would have been the intended message of any clinician asked to comment. The company provided several points in support of the biological plausibility of time varying treatment effects within the network of evidence in the CS (CS p71-72), specifically: • The different timepoints at which surgery occurred for each comparator • The use of adjuvant pembrolizumab in the pembrolizumab arm, which has been shown to be clinically effective in the adjuvant setting in KEYNOTE-091 (as well as being the treatment of choice in advanced NSCLC based on multiple phase 3 RCTs). IMpower010 (NICE TA823), an adjuvant NSCLC trial of an immunotherapy with a similar	The EAG has amended the wording as suggested.

		MoA to pembrolizumab was also positive. • That it is routine for NICE appraisals of oncology treatments to consider hazards to be non-proportional within studies, as evidenced by the independent survival modelling of trial arms. • [redacted] • [redacted]	
"…reliability of results is uncertain due to the subjective nature of the model selection process" (p13)	MSD suggest to remove "…due to the subjective nature of the model selection process".	The EAG's statement implies that the methods used by MSD to select the models used in the time-varying NMA are non-standard and are more subjective than is usual. However, model selection was performed based on statistical and visual fit, using standardised approaches, and full rationale is provided in the CS. MSD note that a degree of uncertainty relating to model selection is also present when time-constant HRs are used, which is	This is not a factual error. The EAG has outlined concerns with the company's time varying NMAs on page 52 of the EAR. No change required.

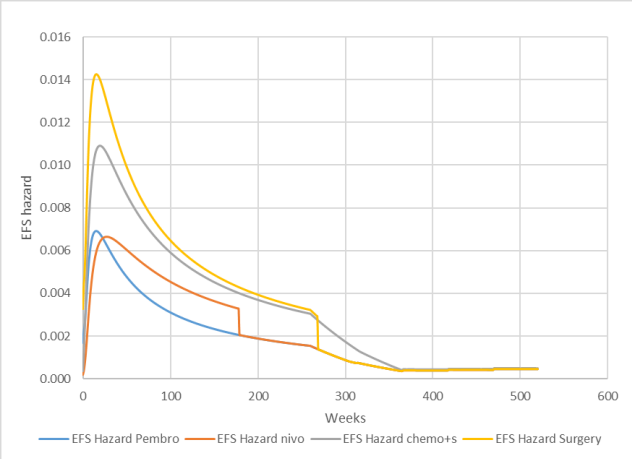
		complicated by the necessity to assume proportional hazards. Therefore, the statement should be amended to provide a more balanced view of the limitations of the time-constant approach.	
"The EAG highlights that, as there is no evidence that the PH assumption was violated in either the KEYNOTE-671[17] trial or in theCheckMate-816[22] trial the company time-constant EFS HR results can be used to inform decision making." (p53)	MSD suggest removing "as there is no evidence" and replacing with "as the proportional hazard assumption tests were not statistically significant". Then adding "however, as acknowledged early in the report, there are limitations with the standard tests for assessing PH." It would also be helpful to highlight that the trends in hazard ratios between the trials are consistently heading in opposite directions, that the proportional hazards assumption is extremely strong and is very rarely used for within-trial analyses in HTAs of oncology treatments (where it is absolutely routine to fit independent survival curves	The company's view is that the EAG is overstating the relevance of the null hypothesis in proportional hazards testing as it applies to decision-making in economic modelling. Although sometimes useful as a summary statistic or simplifying assumption within models, proportional hazards is a strong assumption that should not be expected to hold by default in a meaningful sense, unless by coincidence or in instances where there is obvious biological plausibility. There is no biological rationale supporting hazards being approximately proportional in immunotherapy trials, whereas many arguments can be made in support of the biological plausibility of non-proportional hazards (e.g. CS p71-72, p178). HTAs of oncology treatments now routinely consider hazard functions as they have been observed rather than what they might be under a set of unrealistic constraints, such as proportional hazards. The company considers that there is no obvious reason why HTA bodies should routinely consider within-trial treatment effects as non-proportional and indirect treatment effects to be proportional	This is not a factual error. The EAG does not consider that a comparison of hazard ratios over time between trials is informative as hazards are only required to be proportional between the treatment arms within each study included in the network. No change required.

	along with their implied time-varying treatment effects). It would be helpful if the EAG highlighted any methodological guidance that states that HTA bodies should consider between-trial hazards in ITCs to be proportional unless the proportional hazards assumption is violated or otherwise change the text to state that there is no guidance supporting the primacy of one approach or another and that each should be debated on its own merits (e.g. observed data and biological plausibility).	and feel the EAG's critique should be updated to reflect a more equivocal position between the available methods.	
"The EAG acknowledges the limitations of the standard tests for assessing PH. However, the EAG does not consider that the company has provided a sufficiently strong rationale to support the view that time-varying HR EFS	"The EAG acknowledges the limitations of the standard tests for assessing PH. Without meeting the comparatively high bar of failure of formal proportional hazards testing across all pairwise comparisons in the network, the most appropriate method for indirect treatment comparison (time-varying or	The EAG has not cited methodological guidance suggesting that proportional hazards should be considered more biologically plausible and more suitable for economic modelling unless definitively proven otherwise, which appears to be the suggestion here. It would be helpful for stakeholders if the EAG changed the text to be more equivocal or to cite methodological guidance on the level of evidence that is necessary for one	This is not a factual error. No change required.

NMA results are more informative than time-constant HR EFS NMA results." (p52)	time-constant) should be determined by considering biological plausibility along with the shape of the hazard functions observed in the trials."	methodology or another to be considered the most relevant for decision-making in HTA. Alternatively, it would be helpful if the EAG would state why they believe it is more biologically plausible for hazards within this network of evidence to be considered exactly proportional, rather than to more closely follow their observed within-trial trends.	

Issue 2 Application of instantaneous HR of 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"When comparing the clinical effectiveness of periadjuvant pembrolizumab versus neoadjuvant nivolumab with chemotherapy and versus surgery alone, apply a HR of 1 to the periadjuvant pembrolizumab EFS curve after 41.4 months and 64 months respectively." (p14) "EAG scenarios: (i) Use time-varying HRs but apply a HR of 1 to the	MSD suggest that the EAG make it clear that this assumption has been included in order to be conservative and is jarringly different to the trend in the observed relative hazard functions in the trials. Alternatively, the EAG could instead present a scenario where the HR gradually trends to 1, rather than instantaneously applying a HR of 1 at the end of trial follow-up. The company examined this scenario in the CS	Applying an instantaneous HR of 1 at the end of the comparator trial follow-up is biologically implausible and unreasonably biases the results of the model against pembrolizumab. The implications of this analysis are illustrated by viewing the hazards of each comparator over time as they relate to one another:	The EAG notes that the figure presented by the company does not correspond to the observed trial hazard rates but the modelled hazards for each treatment based upon the company's time-varying HRs. The EAG also highlights that in the EAG's preferred base case, there are no sharp kinks visible in any of the survival curves as implied by the company's figure.

pembrolizumab EFS curve after a given time period for each trial" (p78) "There is no evidence to support periadjuvant pembrolizumab having a sustained treatment effect on EFS beyond the KEYNOTE-671 trial follow-up period. The EAG therefore considers that, rather than using the last time-varying EFS HR estimate for the remaining time horizon, it is more appropriate to apply an EFS HR of 1 to the pembrolizumab EFS curve for the time period that HRs have not been generated." (p82)	(Scenarios 11, 13, 31, 32, p179) and would note that a gradual attenuation of benefit is much more philosophically in line with the way NICE committees have preferred to hedge against uncertainty in survival extrapolations in previous NICE appraisals of immunotherapies.	 This figure has been generated using the Time-varying hazard ratios because the hazard functions generated using these give a more faithful representation of the observed hazard functions within the trials. The company's view is that instantaneous equalisation of hazards is an extreme scenario for the EAG to have included in its base case and, as can be seen in the graph, is jarringly different from the trends in the empirical data. If the EAG wish to explore the impact of reducing the treatment benefit of pembrolizumab in the long term, MSD suggest applying a gradual decrease such that the HR trends to 1 over time. The functionality to implement this is already present in the model and has been explored by the company	The EAG considers the company scenarios that trend the HR to 1 over time to be plausible but the assumptions relating to the time period and rate at which the HRs trend to 1 are arbitrary. The EAG considers that the presence of a kink or otherwise in survival curves does not inform whether extrapolations are likely to provide more reliable or accurate cost effectiveness results and scenarios that explore an apply an instantaneous HR of 1 should also be considered.

		in scenario analyses (CS p179-182, scenarios 11, 13, 31 and 32).	

Issue 3 Implementation of cure

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"In the company model, patients who remain event-free at 5 years have a zero probability of progression to the LR/P health state or progression to the DM health state, and the probability of death is set equal to general population mortality" (p15)	MSD suggest editing this content to reflect the implementation of cure applied in the model.	Cure is implemented gradually over 5-7 years. In addition, only 95% of patients are considered cured at 7 years, therefore, the probability of transitioning from the EF to the LR/P or DM states is never zero and the overall probability of transitioning from EF to death remains higher than the general population mortality.	Thank you. The EAG has amended the text in the EAR as follows: "In the company model, a proportion (95%) of patients who remain event-free at 5 years are assumed to be cured such that the probability of progression to the LR/P or DM health states for these patients is zero by year 7, and the probability of death is equal to general population mortality by year 7."
"In the company model, patients who remain event-free after 5 years are considered cured." (p64)			"In the company model, a proportion (95%) of patients who remain event-free after 5 years are considered cured."
"However, due to mature KEYNOTE-671 trial EFS data (median follow-up 62 months) and the assumption that the probability of			"However, due to mature KEYNOTE-671 trial EFS data (median follow-up 62 months) and for patients assumed to be cured, the probability of

transitioning out of the event-free health state is zero after 5 years, choosing alternative distributions only has a small impact on cost effectiveness results." (p77)			progression from the event-free health state is zero by year 7, choosing alternative distributions only has a small impact on cost effectiveness results."
"in the model, for all patients who remain event-free for ≥5 years, the probability of disease progression is zero and the probability of death is the same as that for the age- and sex-matched general population." (p81)			"in the model, for 95% of patients who remain event-free at 5 years, by year 7 the probability of disease progression is zero and the probability of death is the same as that for the age- and sex-matched general population."
"In the company model, patients who remain event-free at 5 years have a zero probability of progression to the LR/P health state or progression to the DM health state…" (p83)			"In the company model, for 95% of patients who remain event-free at 5 years, the probability of progression to the LR/P or DM health states was set equal to zero by year 7…"

Issue 4 Reporting of pCR stopping rule scenario

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"Clinical advice to the company is that patients who achieve a pCR after surgery should not continue treatment." (p21) "Clinical advice to the company was that treatment should be stopped for patients who achieve pCR after surgery." (p61)	"Clinical advice to the company is that patients who achieve a pCR after surgery **would likely** not continue treatment." "Clinical advice to the company was that treatment **would likely** be stopped for patients who achieve pCR after surgery."	The EAG's text overstates the clinical advice received by the company. The quote from the advisory board report is: "The advisors agreed that treatment would likely be stopped for patients who achieve pCR following surgery by the NHS."	The EAG has amended the wording as suggested.
"Subgroup analyses investigating the use of pembrolizumab before or after surgery are not available as the KEYNOTE-671 protocol mandated that all patients who underwent surgery continued to receive adjuvant pembrolizumab." (p24)	MSD suggest supplementing this statement to specify that this subgroup was addressed via scenario analyses.	Following the decision problem meeting, MSD's understanding of NICE's interest in this subgroup was that NICE wished to see an analysis assessing the cost-effectiveness of periadjuvant pembrolizumab if adjuvant treatment with pembrolizumab was not continued in the group achieving pCR. MSD provided this scenario (CS Table 73, p181, rows 24-26) and therefore consider this scenario relevant to inform the subgroup analysis specified in the scope.	The EAG has amended the wording as suggested.

"Further, clinical advice to the company (CS, p30), and published literature,[18] is that patients who achieve a pCR are considered unlikely to benefit from continued immunotherapy." (p26)	MSD suggest softening the statement to better reflect the advice received, e.g.: "Further, clinical advice to the company (CS, p30), and published literature,[18] is that patients who achieve a pCR may be less likely to benefit."	The current text overstates the advice received by the company. The quote from the advisory board report is: "The advisors agreed that treatment would likely be stopped for patients who achieve pCR following surgery by the NHS." No reference was made around potential to benefit from further immunotherapy after achieving a pCR.	The EAG has amended the wording as suggested.
"The company has carried out three scenario analyses to explore the effects of not using pembrolizumab in the adjuvant setting ..... and therefore results from these scenarios are not useful." (p61)	Suggest deleting "and therefore results from these scenarios are not useful" and replacing with "It is obvious that, if pembrolizumab were not used in the adjuvant setting among patients who achieved a pCR, the ICER estimates would be reduced compared to the base case analysis. This is because the costs of treating a pCR patient are the same (see company model for exact data) but the Number Needed to Treat (NNT) to prevent a recurrence is much higher than in the non-pCR group as absolute recurrence rates are much lower. The company's scenario analysis provides a useful upper estimate of the extent to which the model over-estimates the ICERs versus what might be expected in real world	"Is not useful" reads as a statement of fact and should, at the very least be made clear it is an opinion and that opinion should be justified. The company disagrees with the EAG's opinion on this matter. This is an important scenario analysis and the company believe that it is in the interest of stakeholders that its strengths and limitations with respect to decision-making be described in detail. This scenario is not unlike an adjustment for a subsequent treatment that is not available on the NHS, which is a routine technique used in NICE appraisals of oncology treatments. The company have approximated this scenario by removing the costs of adjuvant treatment [redacted]	The EAG has amended the wording as follows: "The company has carried out three scenario analyses that removed the cost of pembrolizumab in the adjuvant setting for patients achieving a pCR (CS, Table 11, scenarios 24, 25 and 26). The EAG considers that removing the costs of adjuvant pembrolizumab treatment without any corresponding adjustment to effectiveness data will slightly overestimate the clinical and cost effectiveness of periadjuvant pembrolizumab. Further, clinical advice[65] to the company is that whilst adjuvant treatment would

	usage of the regimen in the NHS. In this scenario, it is assumed adjuvant treatment does not prevent any recurrences [redacted]	[redacted]	likely be stopped for patients who achieve a pCR after surgery, pCR status is not currently used in clinical decision-making. The EAG therefore considers that results from these scenarios are currently of limited value for decision-making."

Issue 5 Textual errors and clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Row labels in column 1 of Table E have been transposed (p17) Row labels in column 1 of Table 43 have been transposed (p90)	Please swap the row labels for periadjuvant pembrolizumab and surgery alone so that they align with the correct corresponding results.	Labels have been transposed and do not correspond to the correct cost and QALY results.	Thank you. The typo has been fixed.
Typographical error of Q6W abbreviation: "The recommended dose of pembrolizumab is either 200mg every 3 weeks (Q3W) or 400mg every 6 weeks (6QW)" (p18)	"The recommended dose of pembrolizumab is either 200mg every 3 weeks (Q3W) or 400mg every 6 weeks (**Q6W**)"	For accuracy.	Thank you. The typo has been fixed.

"The treatment regimen[9] in the neoadjuvant setting is either, four cycles of pembrolizumab (200mg) Q3W or two cycles of pembrolizumab (400mg) Q6W. Treatment should be…"(p19)	MSD suggest amending the text to read: "….cycles of pembrolizumab (200mg) Q3W or two cycles of pembrolizumab (400mg) Q6W, given in combination with cisplatin plus gemcitabine or pemetrexed. Treatment…."	To clarify that pembrolizumab is given with platinum-based chemotherapy in the neoadjuvant phase.	Thank you. The text has been changed as suggested.
"The recommended dose of KEYTRUDA in adults is either 20mg Q3W…" (p27)	"The recommended dose of KEYTRUDA in adults is either **200mg** Q3W…" (p27)	This is a typographical error, the correct dose of pembrolizumab is 200mg Q3W or 400mg Q6W.	Thank you. The typo has been fixed.
"One RCT[22] provided evidence for the comparison of periadjuvant nivolumab with chemotherapy versus neoadjuvant chemotherapy". (p27)	"One RCT[22] provided evidence for the comparison of **neoadjuvant** nivolumab…"	Incorrect description of comparator intervention.	Thank you. The error has been fixed.
Dosages administered in the trial are not stated in Table 3 (p33)	Please clarify that the pembrolizumab dose used in the trial was 200mg Q3W.	For clarity.	Thank you. The table has been amended as suggested.
"The company considered that neoadjuvant nivolumab with chemotherapy, adjuvant platinum-based chemotherapy and active monitoring…" (p42)	"The company considered that neoadjuvant nivolumab with chemotherapy, **neoadjuvant** platinum-based chemotherapy and active monitoring…"	Typographical error.	Thank you. The error has been fixed.

“Based on statistical fit, the company considered that, for the neoadjuvant chemotherapy arm combinations, the lognormal distribution under Approach 1, and the Gompertz distribution under Approaches 2 and 3, produced the lowest mean standard errors (MSEs).” (p63)	“Based on statistical fit, the company considered that, for the neoadjuvant chemotherapy arm combinations, **modelling the EF→death transition using** the lognormal distribution under Approach 1, and the Gompertz distribution under Approaches 2 and 3, produced the lowest mean standard errors (MSEs).”	This sentence relates specifically to the modelling of the EF→death transition. MSD suggest this is clarified for avoidance of doubt.	The wording has been amended as suggested.
“The company excluded 59 combinations of parametric distributions based on visual fit. Of the 18 combinations remaining…” (p63)	“The company excluded **49** combinations of parametric distributions based on visual fit. Of the 18 combinations remaining…”	This is a typographical error, it should state that 49 combinations were excluded (67 − 18 = 49) based on visual fit.	Thank you. The typo has been fixed.
Page numbering has broken at p69	-	For ease of use.	Thank you. The page numbering has been fixed.

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
Pg 40	The EAG report states: The EAG considers that, based on KEYNOTE-671 trial EORTC-QLQ-C30 and EQ-5D VAS data, HRQoL trends in the	The EAG considers that, based on KEYNOTE-671 trial **EORTC-QLQ-C30 data, HRQoL trends i**n the neoadjuvant phase	The EAG has removed reference to the EQ-5D VAS scores as suggested (p40):

	neoadjuvant phase (reduced QoL) and adjuvant phase (stable scores) were similar for patients in the pembrolizumab and placebo arms; HRQoL scores did not differ significantly between the trial arms. EQ-5D VAS data are marked as CiC in the CS and therefore should be marked as CiC in the EAR.	(reduced QoL) and adjuvant phase (stable scores) were similar for patients in the pembrolizumab and placebo arms; HRQoL scores did not differ significantly between the trial arms. MSD suggest either removing reference to the EQ-5D VAS scores or marking the described trends as CiC. MSD's preference is to remove reference to the EQ-5D VAS scores.	"The EAG considers that HRQoL trends in the neoadjuvant phase (reduced QoL) and adjuvant phase (stable scores) were similar for patients in the pembrolizumab and placebo arms; HRQoL scores did not differ significantly between the trial arms."

(Please add further lines to the table as necessary)

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Single Technology Appraisal

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID5094]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Wednesday 24 July.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

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Part 1: Treating resectable non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Toby Talbot
2. Name of organisation	Royal Cornwall Hospitals NHS Trust
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with resectable non-small-cell lung cancer? ☐ A specialist in the clinical evidence base for resectable non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for resectable non-small-cell lung cancer ?	The main aim is cure.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	The aim of treatment is to reduce risk of recurrence following surgery so there would be no evaluable tumour, by definition. Event free survival (EFS) is recognised as the surrogate for overall survival with adjuvant/neoadjuvant survivcal. Complete or major pathological (based on pathological assessment of the resected cancer) response seem to be a good predictor for a better outcome.
10. In your view, is there an unmet need for patients and healthcare professionals in resectable non-small-cell lung cancer ?	There is access to neoadjuvant chemoimmunotherapy currently within the NHS in England and also adjuvant immunotherapy for some patient groups (eg PDL1 >50%). Despite recent survival gains with those treatments, there remains a significant risk of subsequent relapse leading to death from metastatic disease. There remains a need to improve survival in those patients undergoing curative intent surgery for non-small cell lung cancer.
11. How is resectable non-small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	NICE guidance (NG122) “Lung cancer: diagnosis and management” published 28 March 2019; last updated 08 March 2024. Pathway of care is well defined and as far as I know, there is little variation across the NHS in England. Presentation of lung cancer may move to increased diagnosis at earlier stage disease due to roll out of Targeted Lung Heath Checks (TLHC) which may impact on the number of patients eligible for this technology. The proposed technology would not have a material impact on the current pathway of care; neoadjuvant and also adjuvant immunotherapy based treatments are in established practice already.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	This technology is similar to treatments already in use in the NHS in England (neo-adjuvant chemo-immunotherapy using Nivolumab (TA876); Adjuvant immunotherapy using Atezolizumab for patients with resected NSCLC with PDL1 >50% (TA823)) so similar if not identical treatment pathways should be well established in the relevant treating centres.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This technology would be delivered through approved specialist treatment centres (Systemic Anti-Cancer Therapy (SACT) units. No new facilities would be required.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	There are no direct head-to-head trials to determine benefits over current standard of care (assuming standard of care is chemo-Nivolumab as per TA876). The addition of adjuvant treatment to neo-adjuvant is possibly advantageous in patients with an incomplete or poor pathological response by extending exposure to immunotherapy. It is not clear what benefit the additional adjuvant immunotherapy may provide to those patients with a complete pathological response; this group is known to have a better chance of cure already based on results from the Keynote671 and Checkmate816 trials.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No – there were no clear subgroups within the published data for whom treatment was much better than chemotherapy and placebo.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	There may be some advantages to patients with this technology as the immunotherapy agent Pembrolizumab is available as a 6 weekly infusion (note the treatment schedule was 3 weekly in the Keynote671 trial) which reduces frequency of visits compared to other currently available immunotherapy agents.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I would expect stopping rules to be within the product licence and reflect the clinical trial protocol (4 cycles of 3 weekly neoadjuvant chemoimmunotherapy then up to 13 cycles of 3 weekly adjuvant Pembrolizumab or 6-7 cycles of 6 weekly Pembrolizumab)
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Preventing relapse of cancer will inevitably result in improved health-related benefits by avoiding the deleterious symptoms of metastatic cancer, toxicity of required treatment for advanced disease and shortened prognosis.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This technology would be an addition to similar treatments already in use (as outlined above) so cannot be considered a "step-change" in the management of resectable non-small cell lung cancer. The use of adjuvant immunotherapy following neo-adjuvant chemoimmunotherapy is not in clinical use currently and may be an advantage over neoadjuvant chemoimmunotherapy alone, particularly in those patients with an incomplete pathological response.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Immunotherapy and chemoimmunotherapy are in widespread use as treatment for lung cancer with well established expertise in toxicity management. I would not anticipate any new issues with this technology.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	The Keynote671 was a large, global clinical trial which included six recruiting sites from within the UK. The ethnicity within the trial was varied due to sites with multiple countries contributing including around 39% from East Asia. The largest ethnic group was white (61.3%), followed by Asian (31.2%). Any ethnicity effects would be minimal in my opinion and therefore results are applicable to the UK setting.

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Event Free Survival (EFS) is considered gold standard for adjuvant/neoadjuvant studies and is recognised as a reliable surrogate for Overall Survival (OS) EFS and OS were collected and published in the Keynote671 trial. Adverse events were entirely in line with clinical experience and expectations with no new or unexpected safety signals
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 876?	No
23. How do data on real-world experience compare with the trial data?	I am unaware of any real-world data. This technology is not in routine use in the NHS.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. 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. Please state if you think this evaluation could	No – I do not believe that this technology would disadvantage any groups of people

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	
25. Do you consider that the KEYNOTE-671 is generalisable to the population who would have perioperative pembrolizumab in NHS clinical practice? Please see EAG report Key Issue 2 for details.	Yes – please see text above in point 20.
26. Do you consider event-free survival to be a reasonable surrogate outcome for overall survival? Please see EAG report Key Issue 3 for details.	Yes – please see text above in point 20.
26. Do you consider that there would be any treatment effect waning after people stop perioperative pembrolizumab and if so could you comment on the timings of this?	Probably. The benefits of immunotherapy can be idiosyncratic based on data and clinical experience from the advanced disease setting in lung cancer and many other malignancies; some patients experience highly sustained benefits, potentially indefinitely where others experience treatment failure. There are few,if any confirmed predictive factors for those who may or may not benefit. Given

Please see EAG report Key Issue 5	this experience I think it is like that waning effects would be not “step like” but gradual waning over year is more likely.

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Part 2: Key messages

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

There remains a need to improve survival and cure rates in patients undergoing curative intent surgery for NSCLC

This technology would be in addition to established treatments

The presence of adjuvant immunotherapy may be of particular benefit to those patients in whom poor or major pathological response is seen

The adjuvant immunotherapy component may be less useful for patients with a complete pathological response

The option of 6 weekly Pembrolizumab may provide a capacity gain for SACT units

Thank you for your time.

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