NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]

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 Eli Lilly:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Roy Castle Lung Cancer Foundation
   b. Royal College of Pathologists

4. **External Assessment Report** prepared by Kleijnen Systematic Reviews (KSR)

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

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Dr Shobhit Baijal, Consultant Medical Oncologist – clinical expert, nominated by British Thoracic Oncology Group & NCRI/RCP/RCR/ACP

8. **External Assessment Report critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews (KSR)
   a. Main critique
   b. Cost-effectiveness results including updated PAS

9. **NICE Managed Access Feasibility Assessment**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Selpercatinib for untreated *RET* fusion-positive advanced non-small-cell lung cancer [ID4056]

Document B

Company evidence submission

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Abbreviations

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AESI	Adverse event of special interest
AFT	Accelerated failure time
AIC	Akaike information criterion
AKT	Protein kinase B
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATEZ	Atezolizumab
AUC	Area under curve
BEV	Bevacizumab
BIC	Bayesian information criteria
BICR	Blinded independent committee review
BID	Twice daily
BNF	British nation formulary
BOR	Best objective response
BSC	Best supportive care
CAMR	Camrelizumab
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CEA	Carcinoembryonic antigen
CEMIPL	Cemiplimab
CGDB	Clinico-Genomic database
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CMU	Commercial Medicines Unit
CNS	Central nervous system
CR	Complete response
eCRF	Electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
DIC	Deviance information criterion
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DURV	Durvalumab
ECG	Echocardiograms
ECOG	Eastern Cooperative Oncology Group
EAG	External assessment group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ	European Platform of Cancer Research Quality of Life Questionnaire
EoT	End of treatment
EPAR	European public assessment report
FE	Fix effect
FISH	Fluorescence in-situ hybridisation
GEM	Gemcitabine
GP	General practitioner

HCRU	Health care research unit
HRQoL	Health-related quality of life
HSE	Health Suvey for England
HSUV	Health state utility value
HTA	Health technology appraisal
IAS	Integrated Analysis Set
ICER	Incremental cost-effectiveness ratio
ICERS	Incremental cost-effectiveness ratios
IPD	Individual patient data
IPI	Ipilimumab
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intention to treat
JAK	Janus kinase
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma
LPS	Lansky Performance Score
LTFU	Lost to follow-up
LYG	Life years gained
MAPK	Mitogen-activated protein kinase
MHRA	Medicine and Healthcare Products Regulatory Agency
MIT	Market information tool
MKI	Multi-kinase inhibitor
MRI	Magnetic resonance imaging
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
MVH	Measuring and valuing health study
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCT	National clinical trial
NE	Not estimable
NGS	Next generation sequencing
NHB	Net health benefit
NHS	National Health Service
NHSE&I	National Health Service England and Ireland
NICE	National Institute for Health and Care Excellence
NIVO	Nivolumab
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OSAS	Overall Safety Analysis Set
PAC	Paclitaxel
PAS	Patient Access Scheme
PASLU	Patient Access Scheme Liaison Unit
PCR	Polymerase chain reaction
PEM	Pemetrexed
PF	Progression free
PFS	Progression free survival
PH	Proportional hazard
PLAT	Platinum
PPI	Proton pump inhibitor

PPS	Post-progression survival
PR	Partial response
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSM	Propensity score matching
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once daily
QLQ	Quality of life questionnaire
QTcF	QT interval corrected for heart rate using Fridericia's formula
RP2D	Recommended Phase II dose
RAM	Ramucirumab
RANO	Response assessment in neuro-oncology criteria
RBC	Red blood cell
RCT	Randomised control trial
RDI	Relative dose intensity
RE	Random-effects
RECIST	Response evaluation criteria in solid tumours
RET	Rearranged during transfection
ROS-1	C-ros oncogene 1
RWE	Real world evidence
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SAS	Safety Analysis Set
SCE	Summary of Clinical Efficacy
SD	Standard deviation
SEL	Selpercatinib
SFU	Safety follow-up
SINT	Sintilimab
SIREN	Selpercatinib in RET fusion-positive non-small-cell lung cancer
SLR	Systematic literature review
SmPC	Summary of product characteristics
SRC	Safety Review Committee
STAT	Signal transducer and activator of transcription
TEAE	Treatment emergent adverse event
TISL	Tislelizumab
TKI	Tyrosine kinase inhibitor
TMLE	Targeted minimum loss-based estimation
TPS	Tumour proportion score
TSD	Technical support document
TTD	Time to treatment discontinuation
UK	United Kingdom
US	United States
WTP	Willingness-to-pay

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

Summary of selpercatinib in *RET* fusion-positive NSCLC

Advanced *RET* fusion-positive NSCLC

- Lung cancer is the second most common cancer in England.[1] NSCLC accounts for between 80–85% of lung cancer cases, with an upper estimate of 2% of these cases exhibiting *RET*-fusion.[2, 3]
- The prognosis for patients with NSCLC is highly dependent upon disease stage at diagnosis. Owing to the ambiguity of common symptoms, a high proportion of patients are diagnosed at advanced stages. of disease; approximately 70% of patients were diagnosed with advanced disease in England in 2019.
- The five-year survival rate for patients diagnosed in the earlier stages of NSCLC is estimated to be 56.6%; this decreases to 2.9% for advanced disease.[4]
- There is limited data on life expectancy for *RET* fusion-positive patients specifically, although real-world evidence indicates that this may be similar to treatment-naïve patients in the advanced setting with other oncogenic drivers when receiving standard therapy.[5]
- NSCLC represents a humanistic and economic burden on society. Patients diagnosed with NSCLC report lower health-related quality of life scores than the general population.[6, 7] The financial cost of lung cancer to the economy in England was estimated to be £307 million in 2010 through direct (medical) and indirect (loss of productivity) costs to society.[8]
- Selpercatinib is a highly selective RET receptor kinase inhibitor; its targeted nature leads to a high level of efficacy in patients advanced *RET* fusion-positive NSCLC, whilst maintaining a tolerable safety profile.[9]

Clinical pathway and proposed position of selpercatinib

- It is standard clinical practice for patients with identified genetic markers to receive treatments targeted to the genetic marker, however, given that there are currently no treatments recommended by NICE for untreated *RET* fusion-positive NSCLC, patients are currently treated with therapies offered to patients not exhibiting genetic markers[10]
- Selpercatinib would be positioned as a first line treatment option for patients diagnosed with advanced non-squamous *RET* fusion-positive NSCLC.
- In line with feedback received from clinical experts in the pralsetinib appraisal (TA81, feedback received from UK clinical experts consulted as part of the appraisal indicated that patients with a positive *RET* status are initially treated with either pemetrexed with platinum-based chemotherapy or pembrolizumab plus pemetrexed with platinum-based chemotherapy (referred to as pembrolizumab combination therapy throughout the submission) in UK clinical practice.[11]
- As such, the primary comparators for this submission are pemetrexed with platinum-based chemotherapy and pembrolizumab combination therapy.

Unmet need for a novel treatment

- Selpercatinib has previously been recommended for use within the Cancer Drugs Fund (CDF) in patients with pre-treated *RET* fusion-positive NSCLC under NICE TA760.[12]
- Should selpercatinib subsequently be recommended by NICE in the first line setting following this appraisal, it would support the opening-up of a new treatment paradigm in England and Wales in the first line setting and would fulfil an unmet need for highly effective, targeted treatments for treatment-naïve patients with advanced NSCLC whose cancers are driven by an oncogenic *RET* rearrangement.

B.1.1 Decision problem

The objective of this submission is to present the clinical and cost-effectiveness of selpercatinib (Retsevmo®) within its anticipated marketing authorisation for the first line treatment of people with advanced rearranged during transfection (*RET*) fusion-positive, non-small cell lung cancer (NSCLC) who require systemic therapy. Selpercatinib has previously been recommended for use within the Cancer Drugs Fund (CDF) in pre-treated patients under NICE TA760.[12]

Eli Lilly and Company are seeking a positive recommendation for either routine commissioning or funding from the CDF for selpercatinib in *RET* fusion-positive NSCLC for treatment-naïve patients, given the current levels of maturity of the survival data available from LIBRETTO-001.[13] Any uncertainty in the survival data could be addressed through further data-cuts from LIBRETTO-001 or from LIBRETTO-431, an ongoing Phase III randomised controlled trial in treatment-naïve *RET* fusion-positive NSCLC,[14, 15] which will collect further survival data and direct comparative data versus the comparators directly relevant to the decision problem of this submission.

The decision problem addressed within this submission is outlined in Table 1 below.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	• Adults with untreated advanced *RET* fusion-positive non-small cell lung cancer (NSCLC).	• Treatment-naïve patients with advanced non-squamous *RET* fusion-positive NSCLC who require systemic therapy.	• The evidence presented in this submission is for patients with non-squamous histology. This population is in line with the LIBRETTO-001 Phase 1/2 trial (the clinical trial comprising the clinical evidence base for selpercatinib in the submission), where no treatment-naïve patients in the LIBRETTO-001 trial had squamous histology.[13, 16] RET fusions rarely occur in NSCLC tumours with squamous histology,[2] which was acknowledged by the Committee in the previous evaluation for selpercatinib.[12]
Intervention	• Selpercatinib	• Selpercatinib 160 mg twice daily (BID).	• As per the NICE final scope.
Comparator(s)	For people with untreated advanced RET fusion positive NSCLC: • Pralsetinib [subject to ongoing NICE appraisal ID3875] For people with non-squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%:	• Pembrolizumab with pemetrexed and platinum chemotherapy • Pemetrexed and platinum chemotherapy.	• As discussed above, the target population has been restricted to patients with non-squamous histology, in line with the population of the LIBRETTO-001 study. As a result, comparators presented in the pre-invitation scope relevant to the squamous population will not be included in the submission.[16] This approach was discussed and accepted by the Committee for the selpercatinib evaluation for pre-treated NSCLC patients. • In line with clinical experts consulted as part of the recent evaluation of pralsetinib in the same indication, feedback from UK clinical experts

	• Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) with or without pemetrexed maintenance treatment For people with adenocarcinoma or large-cell carcinoma whose tumours express PD-L1 with a tumour proportion score below 50%: • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment • For people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Atezolizumab • Pembrolizumab with carboplatin and paclitaxel (who need urgent clinical intervention) • For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)		consulted by Eli Lilly as part of the evaluation process indicated that, of treatments available for patients with untreated, advanced, non-squamous NSCLC, patients with a positive *RET* status are most commonly treated with either pemetrexed with platinum-based chemotherapy OR pembrolizumab plus pemetrexed with platinum-based chemotherapy.[17, 18] As such, these are the only comparators considered relevant to this submission. • Pralsetinib is not considered a relevant comparator in this population as it has not received a positive recommendation from NICE, and therefore is not be considered part of routine practice.[18]

	• Pembrolizumab with carboplatin and paclitaxel		
Outcomes	The outcome measures to be considered include: • Overall survival • Progression free survival • Response rate • Time to treatment discontinuation • Adverse effects of treatment • Health-related quality of life.	Primary: • Objective response rate (ORR) Secondary: • Duration of response (DOR) • PFS • OS • Time to treatment discontinuation HRQoL: • European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C-30 (QLQ-C30) Safety outcomes: • Adverse events (AEs).	As per the NICE final scope.
Economic analysis	• The cost-effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year. • The time horizon for estimating cost-effectiveness was set at a lifetime horizon to sufficiently reflect any differences in costs or outcomes between the technologies being compared. • Costs are considered from a 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.	• A cost-effectiveness analysis has been conducted for selpercatinib versus relevant comparators. • As per the NICE reference case, cost-effectiveness is expressed in terms of incremental cost per quality adjusted life years (QALYs). Costs are considered from the perspective of the NHS and Personal Social Services (PSS). A lifetime horizon is used to capture all costs and benefits associated with selpercatinib and its comparators.	In line with the NICE final scope.

Subgroups to be considered	If the evidence allows the following subgroups will be considered: • tumour histology (squamous or non-squamous), and • level of PD-L1 expression	The following subgroup analysis are considered: • Subgroups analyses in *RET* fusion-positive advanced NSCLC patients with brain metastases	PD-L1 status was not collected in the pivotal LIBRETTO-001 trial, therefore subgroup analyses of patients based on PD-L1 expression were not able to be performed. In addition, as all treatment-naïve patients with advanced *RET*-fusion positive NSCLC enrolled in the LIBRETTO-001 trial had non-squamous histology, subgroup analyses by tumour histology were similarly not able to be performed. Subgroup analyses were conducted in patients with brain metastases. It has been found that approximately 50% of patients with *RET* fusion-positive NSCLC experience brain metastases therefore subgroup analyses in this population were performed.[19]

Abbreviations: AE: adverse event;; DOR: duration of response; EORTC: European Organisation for Research and Treatment of Cancer; NHS: National Health Service; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PD-L1: programmed death ligand; PFS: progression free survival; PSS: Personal Social Services; QALY: quality adjusted life year; QLQ-30: quality of questionnaire C-30; RET: rearranged during transfection.

B.1.2 Description of the technology being appraised

A description of the technology being appraised (selpercatinib [Retsevmo®]) is provided in Table 2. The draft Summary of Product Characteristics (SmPC) is included in the reference pack and the UK public assessment report is presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Selpercatinib (Retsevmo®)
Mechanism of action	Selpercatinib is a first-in-class, orally available, highly selective small molecule inhibitor of fusion, mutant and wild-type products involving the proto-oncogene RET tyrosine kinase receptor.[20] Administration of selpercatinib inhibits cell growth in tumour cells that exhibit increased RET activity.[20]
Marketing authorisation/CE mark status	A European Commission Decision (approval) for a conditional marketing authorisation for selpercatinib as monotherapy for the treatment of patients with advanced *RET* fusion-positive NSCLC, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy was granted in February 2021.[21] [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The current licensed indication for selpercatinib is as follows: • Selpercatinib as a monotherapy is indicated for the treatment of adults with: ○ Advanced *RET* fusion-positive NSCLC who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy ○ Advanced *RET* fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib • Selpercatinib as a monotherapy is also indicated for the treatment of adults and adolescents 12 years and older with: ○ Advanced *RET*-mutant medullary thyroid cancer who require systemic therapy following prior treatment with cabozantinib and/or vandetanib. [redacted] • [redacted]
Method of administration and dosage	Oral selpercatinib 160 mg (2 x 80 mg capsules) twice daily (BID). Capsules of 40 mg are also available for patients who require dose adjustments.

Additional tests or investigations	An accurate and validated assay for *RET* is necessary for the selection of *RET* fusion-positive patients for treatment with selpercatinib. In England and Wales, Next Generation Sequencing (NGS), which is based on whole genome-sequencing, is becoming the diagnostic standard for oncogenic-driven cancers. The NHS is transitioning to NGS via designated Genomic Hubs across England.[22, 23]
List price and average cost of a course of treatment	The list prices of a 60 hard capsule pack of 80 mg or 40 mg selpercatinib are £4,680.00 and £2,340.00 respectively.[24] At list price, the cost of a 28-day cycle of selpercatinib is £8,736.00.
Patient access scheme (if applicable)	The company has incorporated the existing PAS discount already established in the NHS for selpercatinib.

Abbreviations: BID: twice daily; EMA: European Medicines Agency; MHRA: Medicine and Healthcare Products Regulatory Agency; NGS: Next Generation Sequencing; NHS: National Health Service; NSCLC: non-small cell lung cancer; PAS: Patient Access Scheme; PASLU: Patient Access Scheme Liaison Unit; *RET*: rearranged during transfection.

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

B.1.2.1 Overview of the disease

Disease background

Lung cancer is the second most common cancer in England, accounting for approximately 12% of all new cancer cases, with 40,168 people newly diagnosed with lung cancer in England in 2019.[25] Lung cancer is also the leading cause of cancer-related death in England, with an age-standardised mortality rate for women and men of 43.4 and 61.5, respectively per 100,000 in 2019.[26] As such, lung cancer represents a key clinical and public health challenge.[3, 27]

Lung cancer is termed “primary” when tumours first originate in lung tissue, usually in the cells lining the bronchi and other parts of the lung (e.g. bronchioles or alveoli). Lung cancer is divided into two main subtypes based upon the microscopic appearance of the tumour cells: small cell lung cancer and non-small cell lung cancer (NSCLC).[3] These subtypes progress and are treated in different ways, making their distinction clinically important. NSCLC accounts for the majority (80–85%)[28] of lung cancer cases in the UK and can be sub-divided further into three histological groups: adenocarcinoma (the most common subtype in both men and women), large-cell undifferentiated carcinoma and squamous cell carcinoma. Adenocarcinoma and large cell undifferentiated carcinoma comprise 40% and 5–10% of all lung cancer cases, respectively, and are frequently considered together under “non-squamous” histology.[29]

NSCLC can be further classified by genetic markers such as *EGFR* mutations, *ALK* translocation and *ROS-1* rearrangements.[30] *RET* fusion is one such marker, and positive patients account for approximately 1–2% of NSCLC cases. *RET* fusions are most commonly seen in adenocarcinoma, but have also been reported in mixed adenosquamous histology.[2] This is supported by a recent retrospective observational study published by Hess 2021, which found that patients exhibiting metastatic NSCLC with *RET* mutations were more likely to have non-squamous histology than the general NSCLC population, as informed by the Flatiron-Foundation Medicine Clinico-Genomics Database (CGDB) in the United States.[31]

Rearranged during transfection tyrosine kinase

RET is a transmembrane receptor protein tyrosine kinase, which is present on the surface of several tissue types.[2] The RET protein is encoded by the *RET* gene, which under normal circumstances plays a role in cell growth, division and specialisation. Abnormal *RET* activation occurs through two mechanisms associated with malignancy: mutations and fusions, with the latter typically present in NSCLC. Fusions are generated by an inversion of the short and long arms of chromosome 10.[32] Chromosomal rearrangement in this way leads to the joining of a partner gene and the *RET* intracellular kinase domain, which is preserved and activated in the resulting protein.[33]

A number of independent genes have been reported to fuse with *RET;* the most commonly reported fusion partner in NSCLC is *KIF5B*, reported in 50–70% of cases.[2] This leads to abnormal activation of the RET protein and, in turn, downstream signalling in the cell, including activation of MAPK, PI3K/AKT and JAK/STAT pathways.[2] Abnormal *RET* activity enhances cell survival, proliferation, transformation, migration and angiogenesis, making *RET* fusions an important oncogenic driver in NSCLC.[34] *RET* fusions tend to be mutually exclusive with other major lung cancer oncogenic drivers and therefore represent a unique molecular target.[5, 35]

Patients exhibiting *RET* fusion-positive NSCLC share many clinical features with those patients who have tumours driven by other oncogenic mutations, such as *ALK*, *ROS-1* and *EGFR*.[36] Patients with *RET* fusion-positive NSCLC are typically of a younger age (≤65 years) with minimal or no prior history of smoking.[31, 37] Data from a retrospective real-world registry study (IMMUNOTARGET registry, including patients from Europe, the US, Israel and Australia), found that 66.7% of patients with *RET* fusion-positive tumours had never smoked (compared with 6.7% who were current smokers) and that the median patient age was 54.5 years (range: 29–71).[2, 37] *RET* fusions in NSCLC tumours have also been found to be associated with female gender and Asian ethnicity.[2] This patient profile contrasts to other subtypes of lung cancer, which are frequently associated with smoking (72% of lung cancers cases in England are estimated to be attributable to smoking) and older age (44% of new cases of lung cancer occurred in people ≥75 years between 2015–2017 in the UK).[3, 38, 39] Patients with *RET* fusion-positive NSCLC therefore tend to have a better health status than the general NSCLC population.

Studies reporting epidemiological data for *RET* fusion-positive NSCLC are limited in number and by geography, with no studies reporting the prevalence of *RET* fusion-positive NSCLC patients in the UK. Consequently, epidemiological data for *RET*-fusion positive NSCLC specifically in the UK are currently restricted to estimates using available statistics. Using data from the Office of National Statistics, the National Lung Cancer Audit database, Cancer Research UK, Royal College of Physicians and an upper estimate of 2% from Kohono *et al*. 2012, approximately 250 patients are estimated to have advanced non-squamous NSCLC exhibiting a *RET* fusion molecular subtype in England.[2, 40-42]

Disease progression and prognosis

The prognosis for patients with NSCLC is highly dependent upon disease stage at diagnosis. NSCLC can be categorised into four principal stages, with Stages IIIB–C (the cancer is 5–7 cm in size and has spread to lymph nodes, different lobes of the lungs and/or other organs in the chest as a single or greater than one tumour) and IV (the cancer has spread to both lungs and/or other parts of the body) grouped under the classification “advanced”.[43, 44] The five-year survival rate for those diagnosed in earlier stages of NSCLC disease is estimated to be 56.6%, which decreases to 2.9% for those diagnosed at advanced stages.[4] At earlier stages of disease, curative surgery

remains a treatment option, whilst at advanced stages of disease systemic therapies are used to delay progression and extend survival for as long as possible.[30]

A high proportion of NSCLC cases are currently diagnosed at an advanced stage in England (70% of patients were diagnosed with Stage III and IV disease in 2019), primarily because of the ambiguity of common symptoms, which include fatigue, loss of appetite, chest pain, weight loss and respiratory problems.[25] Untreated NSCLC is characterised by rapid growth and progression to more advanced stages of disease, with a small untreated tumour lesion typically taking <1 year to progress to advanced disease, serving to compound the effects of delayed diagnosis.[45, 46] As a result, prognosis for lung cancer on the whole is poor, with only 37% of patients surviving >1 year following diagnosis between 2012–2015, compared with >95% of English patients with a breast or prostate cancer diagnosis.[47-50]

There is limited published data on the survival of patients with advanced *RET* fusion-positive NSCLC. The IMMUNOTARGET registry (Mazieres et al. 2019) examined patients diagnosed with advanced NSCLC with a range of different molecular subtypes, including *RET* fusion, treated with first- or second-line immunotherapy (N = 551 from 10 countries).[37] Median PFS ranged between 2.1–3.4 months, whilst median OS ranged between 10.0–21.3 months.[37] The study reported the joint lowest median PFS (2.1 months) and the highest median OS (21.3 months) for *RET* fusion-positive NSCLC, but values remained within the range of other oncogenic drivers.[5, 37] Similarly, in an observational study by Hess *et al.* (2021) carried out in 46 *RET* fusion-positive patients receiving pembrolizumab plus platinum based chemotherapy in the first line, the median PFS was found to be 6.6 months.[31] In comparison, studies reporting treatment using selective *RET* tyrosine kinase inhibitors (TKIs), including selpercatinib, reported longer median PFS (treatment-naïve: 15.6 month; pre-treated: 12.2 months)[51] and median OS durations (treatment-naïve and pre-treated population: 49.3 months),[52] relative to patients treated with immunotherapies in the real world setting.

The general characteristics of patients with *RET* fusion-positive NSCLC (i.e. younger age, non-smoking status, better tumour performance score) may be expected to have a prognostic impact on survival. However, based on current evidence the real prognostic influence of *RET* mutations remains unclear.[31] An analysis reported by Hess et al. 2021, who assessed tumour response outcomes in 5,807 NSCLC patients (*RET* positive: 46; *RET* negative: 5,761) in the United States using data from the Flatiron CGDB, found that there was no significant difference in PFS between patients with *RET* fusions and patients without (p=0.06), but that OS did differ significantly (hazard ratio [HR]: 1.91; 95% CI: 1.22–3.0; p=0.005).[31] However, after adjusting for baseline covariates, there was no statistically significant difference identified for either PFS (HR: 1.24; 95% CI: 0.86–1.78; p=0.25) or OS (HR: 1.52; 95% CI: 0.95–2.43; p=0.08) in patients treated with standard therapy prior to the availability of selective *RET* inhibitors.[31] While acknowledging the limitations of this study, such as the small sample size of the *RET* fusion-positive population and potential unmeasured confounding, the lack of statistically significant difference in adjusted survival outcomes by *RET* status provides early evidence that *RET* fusion may not be inherently prognostic.

Burden of disease

NSCLC represents a humanistic and economic burden on society. Disease symptoms caused by NSCLC, and the various therapies used to cure or manage them, impact the emotional and physical functioning of patients.[53, 54] However, there is a paucity of data on the HRQoL impact of *RET* fusion-positive NSCLC specifically. As such, these data presented relate to NSCLC,

regardless of genomic alteration and/or biomarker expression, although they are anticipated to reflect the experience of patients with *RET* fusion-positive NSCLC.

The symptomatic and HRQoL burden of NSCLC are closely related. The earliest stage of NSCLC is often asymptomatic.[55] However, as NSCLC progresses, patients experience greater symptom burden and subsequently lower quality of life (QoL).[56] Common physical symptoms of NSCLC include fatigue (98%), loss of appetite (98%), respiratory problems (94%), cough (93%), pain (90%) and blood in sputum (70%).[53] At advanced stages, the cancer may spread to the lymph nodes, brain, liver, adrenal glands or the bones, bringing additional symptoms associated with the secondary tumour's location.[57]

Brain metastases occur frequently in patients with *RET* rearrangements, with an estimated lifetime prevalence of 46% in Stage IV disease, resulting in additional symptoms (e.g. confusion, headaches and changes in behaviour), complications to treatment and poorer patient prognosis and quality of life.[58] A real-world evidence study estimated a significantly shorter life expectancy for NSCLC patients with brain metastases (25.3 weeks) compared with patients with metastases in the contralateral lung (50.5 weeks), bone (49.4 weeks), adrenal glands (48.7 weeks) and liver (44.9 weeks) ($p<0.01$ for all comparisons).[59]

In addition to the physical symptoms of NSCLC, a diagnosis of lung cancer, treatment and conversations around prognosis also impact the mental health of patients, with depression reportedly affecting between 23–40% of patients, and anxiety affecting an estimated 16–23% of patients.[53] As a result of this combined impact on their physical and mental wellbeing, patients are increasingly unable to complete activities perceived as "normal" in their family and social roles.[53]

Consequently, the HRQoL in NSCLC patients is lower than in the general population.[6] A 2018 systematic review highlighted that among patients receiving second line treatment for advanced NSCLC, mean EQ-5D scores ranged between 0.53–0.82, with the highest values being associated with tyrosine kinase inhibitor treatment.[6] A similar range was seen among patients being treated for advanced NSCLC, where the treatment line was unspecified (0.53–0.77).[6] EQ-5D scores were worse for patients experiencing disease progression (0.55–0.69), compared with those patients with stable/progression-free disease (0.66–0.76).[6] All scores were lower than the index EQ-5D score, calculated for the English general population (0.85).[7]

The financial cost of lung cancer to the economy in England was estimated to be £307 million in 2010 through direct (medical) costs to the NHS and indirect costs (loss of productivity) to society.[8] Medical expenditure typically includes costs associated with medication, surgery, radiotherapy, follow-up visits and the management of AEs. Neutropenia and granulocytopenia are common adverse events associated with chemotherapy, severe cases for which may require hospitalisation.[60] Treatment costs typically increase with disease stage, with Stage I treatment costs for NSCLC reported at £7,952 per patient in 2014, increasing to £13,078 for Stage IV.[61] Due to the impact of NSCLC on patients' mental and physical health, work life is also negatively affected, leading to indirect costs to society through absenteeism, lost productivity and early retirement.[62]

Selpercatinib

Selpercatinib is a highly selective inhibitor of fusion, mutant and wild-type products involving the proto-oncogene receptor tyrosine kinase RET.[63] The drug acts as an inhibitor that controls the RET kinase enzyme and prevents tumour cell growth.[63] Selpercatinib has shown promising

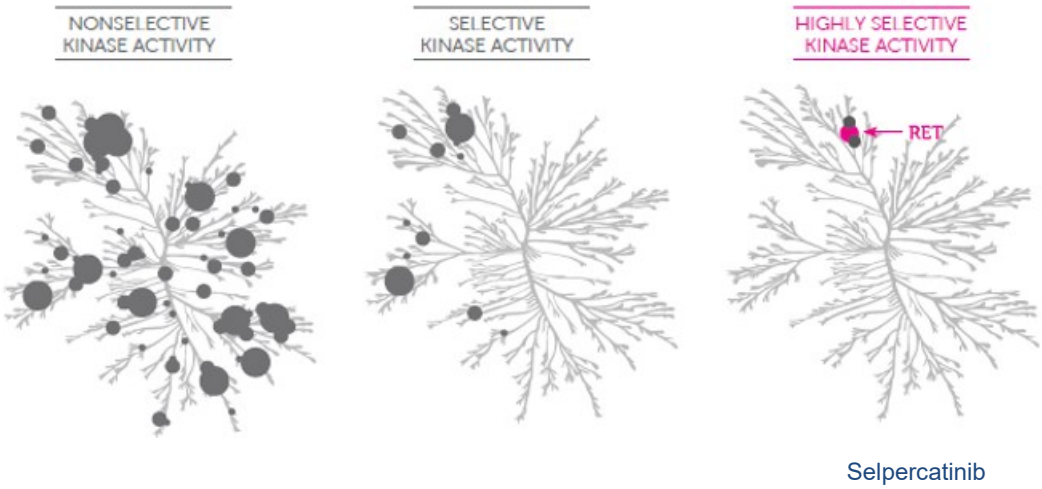
activity in advanced *RET*-positive solid tumours and is approximately 250-fold more selective for RET relative to other kinases (Figure 1).[9] This specificity is anticipated to deliver both robust anti-tumour activity, as well as a more favourable safety and tolerability profile compared to other therapies currently available to treat advanced *RET* fusion-positive NSCLC patients in the UK.[2]

The safety and efficacy of selpercatinib has been assessed during an ongoing open-label single-arm Phase I/II clinical trial (LIBRETTO-001) in patients with advanced solid tumours exhibiting *RET* rearrangements.[64] LIBRETTO-001 commenced in May 2017 with a Phase I dose-escalation study designed to determine the maximum tolerated/recommended dose of selpercatinib. Following Phase I dose-escalation, dose-expansion was initiated as part of Phase II, with treatment-naïve and pre-treated advanced NSCLC patients receiving 160 mg BID, and the anti-tumour activity of selpercatinib analysed.[62, 65] Selpercatinib is also being explored in LIBRETTO-431 (NCT04194944), a randomised, open-label, Phase III trial comparing selpercatinib to platinum-based and pemetrexed therapy, with or without pembrolizumab, as first line treatment for advanced or metastatic *RET* fusion-positive NSCLC.[14]

A European Commission Decision (approval) for a conditional marketing authorisation for selpercatinib as monotherapy for the treatment of patients with advanced *RET* fusion-positive NSCLC, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy was granted in February 2021.[21] Use of selpercatinib was subsequently recommended under the Cancer Drugs Fund (CDF) by NICE in TA760 making it the first RET kinase inhibitor to be available in England and Wales.[12]

The Company have submitted an application to the MHRA for a licence extension for use of selpercatinib in treatment-naïve advanced *RET* fusion-positive NSCLC. Approval of selpercatinib for use in this indication would fulfil an unmet need for a highly effective targeted therapy for treatment-naïve patients with advanced NSCLC whose cancers are driven by an oncogenic *RET* rearrangement.

Figure 1: Representation of different kinase activity and the selectivity of selpercatinib for RET tyrosine kinase



Footnotes: The diagram depicts the activity of different kinases. It highlights that multi-kinase drugs influence a wide variety of kinases, frequently producing adverse side-effects. The specificity of selpercatinib to the RET kinase is anticipated to provide enhanced efficacy and tolerability.
Abbreviations: RET: rearranged during transfection.
Source: Drilon *et al*. (2018).[9]

B.1.2.2 Clinical pathway of care

The treatment of NSCLC in the UK has been assessed by NICE through both published guidelines (NG122) and previous technology appraisals (TAs).[30] Given that at present there are no RET receptor kinase inhibitors recommended by NICE in the treatment-naïve setting,[18] the treatment pathway for *RET* fusion-positive NSCLC described below has been informed by current guidance available from NICE for the treatment of NSCLC more widely.[30]

NICE-recommended treatment pathway for treatment-naïve patients with advanced, non-squamous, *RET* fusion-positive NSCLC

Treatment of NSCLC is dependent on the disease stage at diagnosis, cancer histology (squamous and non-squamous) and the presence/absence of genomic drivers and biomarkers (e.g. PD-L1 status; an immune checkpoint protein expressed on the surface of cancer cells).[3, 30] In England, NGS is becoming the standard diagnostic practice to identify key oncogenic drivers in NSCLC (*EGFR*, *ROS1* and *ALK*).[66] NGS is completed in Genomic Hubs, which allows a panel of genetic mutations, rearrangements and fusions (including *RET*-fusions) to be identified.[23, 66] This expedites the diagnostic process and allow clinicians to use targeted therapies, like selpercatinib, as first line treatment in the advanced setting.

For patients diagnosed with early-stage NSCLC (Stage I–II and usually IIIA), treatments with curative intent are indicated. These include surgery, radiotherapy, chemotherapy and multimodality treatment.[30] However, for patients who present with, or progress to, advanced (Stage IIIB/C or IV) NSCLC, treatments with curative intent are not suitable, and NICE recommends systemic anti-cancer therapies, with treatment choice informed by the histology, biomarkers and genetic markers of the patient's tumour.[30]

It is standard clinical practice for patients with identified genetic markers to receive treatments targeted at that genetic marker, rather than by their other biomarker status (i.e. PD-L1 <50% or ≥50%). However, given that there are currently no treatments recommended by NICE that target *RET* fusion-positive NSCLC at first line,[18] this patient population is currently treated with the same set of therapies as patients not exhibiting genetic markers. This practice is supported by the finding that patients with oncogene-driven NSCLC, such as *RET* fusion-positive, *EGFR*, *ALK* or *ROS-1* positive, typically have just one genetic marker, and thus would not benefit from other oncogene targeted therapies.[10, 62, 67]

As described previously, patients with a *RET* fusion predominantly have non-squamous histology.[2] NICE recommends a number of therapy options for patients without genetic markers presenting with first line (treatment-naïve), advanced, non-squamous NSCLC, as presented in Table 3 and Figure 2. Firstly, NICE recommend treatment with pembrolizumab in combination with pemetrexed and platinum chemotherapy (TA683), which may be offered regardless of patients' PD-L1 status.[68] For patients with a PD-L1 tumour proportion score (TPS) of ≥50%, pembrolizumab monotherapy (TA531) and atezolizumab monotherapy (TA705) are recommended.[69, 70] For patients with a PD-L1 TPS of <50%, atezolizumab in combination with bevacizumab, carboplatin and paclitaxel (TA584),[71] pemetrexed in combination with carboplatin (NG122)[30] and platinum doublet chemotherapy (NG122 or TA181)[30, 72] with or without subsequent pemetrexed maintenance therapy (TA402 or TA190)[73, 74] are recommended.

Feedback received from clinical consultation received as part of this evaluation noted that due to the lack of availability of targeted treatment options for patients with a positive *RET* status, both

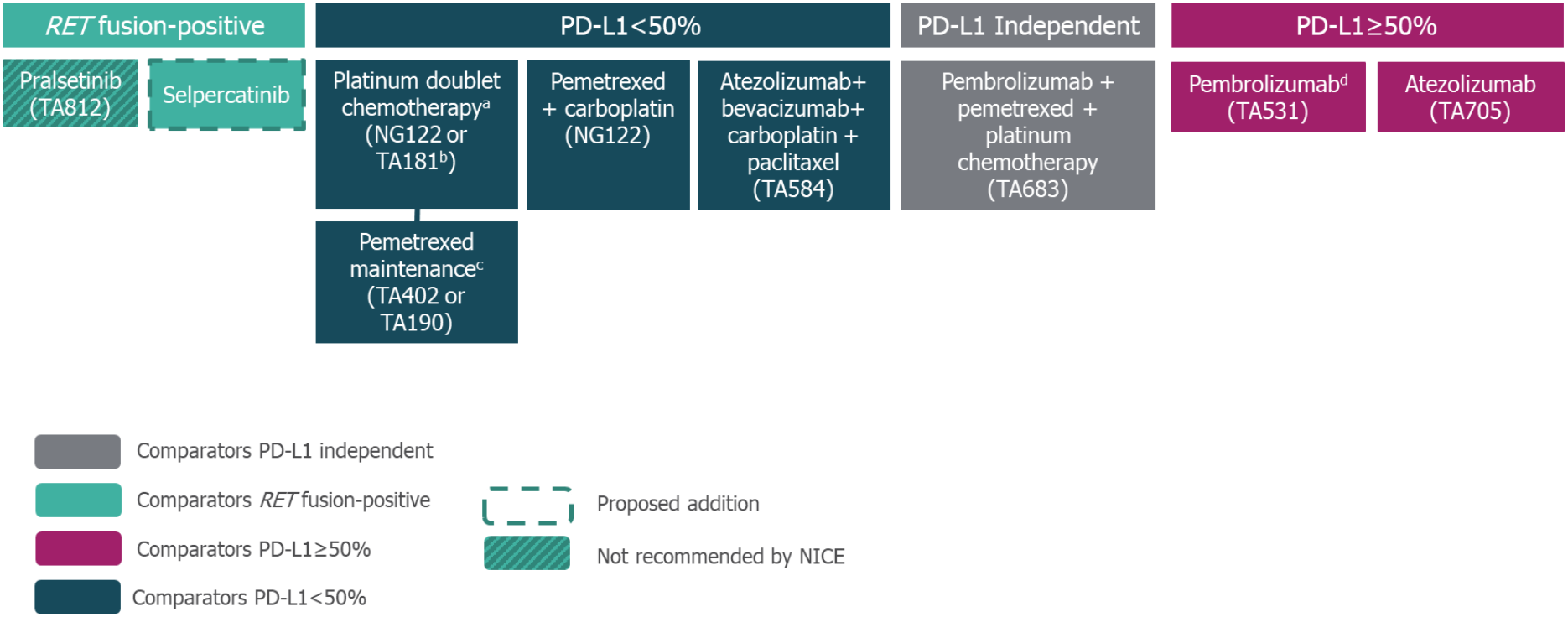
pembrolizumab combination therapy and pemetrexed plus platinum based chemotherapy are commonly used in treatment-naïve *RET*-fusion positive patients.[17]

Table 3: Summary of recommended NICE Technology Appraisal guidance for first line therapies for advanced, non-squamous, NSCLC[18]

NICE guideline or guidance (year published)	Intervention[a]	Population
TA705 (2021)[70]	Atezolizumab monotherapy	Adults with untreated metastatic non-small-cell lung cancer (NSCLC), who have PD-L1 expression on at least 50% of tumour cells or 10% of tumour-infiltrating immune cells and have no *EGFR*- or *ALK*-positive mutations.
TA683 (2021)[68]	Pembrolizumab + pemetrexed + platinum chemotherapy	Adults with untreated, metastatic, non-squamous NSCLC whose tumours have no epidermal growth factor receptor (*EGFR*)-positive or anaplastic lymphoma kinase (*ALK*)-positive mutations.
TA584 (2019)[71]	Atezolizumab + bevacizumab + carboplatin + paclitaxel	Adults with metastatic non-squamous NSCLC who have not had treatment for their metastatic NSCLC before and whose PD-L1 tumour proportion score is between 0% and 49% or when targeted therapy for epidermal growth factor receptor (*EGFR*)-positive or anaplastic lymphoma kinase (*ALK*)-positive NSCLC has failed.
TA531 (2018)[69]	Pembrolizumab monotherapy	Adults with untreated PD-L1-positive metastatic NSCLC whose tumours express PD-L1 (with at least a 50% tumour proportion score) and have no *EGFR*- or *ALK*-positive mutations.
TA402 (2016)[74]	Pemetrexed maintenance	Adults with locally advanced or metastatic non-squamous NSCLC which has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy.
TA190 (2010)[73]	Pemetrexed maintenance	People with locally advanced or metastatic NSCLC other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.
TA181 (2009)[72]	Platinum doublet chemotherapy	In combination with cisplatin is recommended as an option for the first line treatment of patients with locally advanced or metastatic NSCLC only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.

Footnotes: [a] Pralsetinib was assessed in a first line advances setting but did not receive a recommendation
Abbreviations: *ALK*: alkaline phosphatase; *EGFR*: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; PD-L1: programme death ligand 1; TA: technology appraisal.

Figure 2: NICE-recommended treatment pathway for advanced, non-squamous, NSCLC at first line



Footnotes: [a] Platinum doublet chemotherapy may include: platinum-based chemotherapy (carboplatin/cisplatin) + paclitaxel, docetaxel, gemcitabine or vinorelbine; or cisplatin + pemetrexed. [b] TA181 (pemetrexed + cisplatin) and TA347 (nintedanib + docetaxel) recommend technologies in adenocarcinoma and large cell carcinoma, respectively. [c] Pemetrexed maintenance is only permitted after pemetrexed + cisplatin (not carboplatin). [d] Pembrolizumab monotherapy is subject to a 2-year stopping rule.
Abbreviations: PD-L1: programmed death-ligand; NG: NICE Guidelines; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection; TA: technology appraisal.

Positioning of selpercatinib relative to the current treatment pathway

Selpercatinib would be positioned as a first line treatment option for patients diagnosed with advanced non-squamous *RET* fusion-positive NSCLC. Selpercatinib is anticipated to be the first *RET* specific treatment available for untreated patients, and will fulfil a significant unmet need for a targeted, effective treatment in this population.

Accordingly, in clinical practice, selpercatinib is anticipated to substitute first line, non-targeted treatments, which are currently being used in treatment-naïve patients with a positive *RET* status diagnosed in England and Wales. In line with clinical experts consulted as part of the recent evaluation of pralsetinib in the same indication (TA812),[18] feedback from clinical experts consulted as part of the appraisal process indicated that treatment-naïve patients with a positive *RET* status are typically treated with either pemetrexed with platinum-based chemotherapy or pembrolizumab combination therapy in UK clinical practice.[17] Consequently, the primary comparators for this submission are pemetrexed with platinum-based chemotherapy and pembrolizumab combination therapy.

Pralsetinib was not considered a relevant comparator in this population as it has not received a positive recommendation from NICE and therefore may not be considered part of routine practice.[11]

Unmet need for a *RET*-fusion targeted therapy in the current treatment pathway

There are currently no targeted therapies for advanced *RET* fusion-positive patients approved for routine use at first line on the NHS. Treatment-naïve patients with advanced *RET* fusion-positive NSCLC instead receive the same treatment options as those patients with no recognised oncogenic drivers, including immunotherapy and chemotherapy combination options (Figure 2). As outlined in Section B.1.2.1 survival estimates for patients with advanced, *RET* fusion positive NSCLC with immunotherapies remain poor, with PFS estimates below one year and OS approximately two years or less.

The specificity of targeted treatments, like selpercatinib, are anticipated to deliver substantially superior efficacy outcomes compared to non-targeted treatments such as immunotherapies. Indeed, there is evidence to suggest that *RET*-rearranged lung cancers are characterised by low levels of PD-L1 expression, suggesting that these tumours are “biologically cold” and less likely to be highly responsive to immunotherapy relative to other cancers.[75] In addition, adverse events from non-targeted immunotherapies can affect one or several different systemic organ systems, with an incidence of Grade 3 and higher toxicities of 7–13%.[76]

In contrast, as described in Section B.2.5 results from LIBRETTO-001 demonstrate an overall response rate (ORR) with selpercatinib of 84.1% and a median PFS of 21.95 months, with OS not yet estimable. Selpercatinib is also well tolerated, with a safety profile characterised by recognised toxicities easily revered through dose interruption or reduction.[77]

Accordingly, as a RET receptor kinase inhibitor with a high specificity, selpercatinib is anticipated to fulfil a significant unmet need in England and Wales for an efficacious therapy with a tolerable safety profile in treatment-naïve patients with advanced *RET* fusion-positive NSCLC.

B.1.3 Equality considerations

It is not expected that this appraisal will exclude any people protected by equality legislation, nor is it expected to lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population. Similarly, it is not expected that this appraisal will lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Summary of clinical evidence for selpercatinib in *RET* fusion-positive NSCLC

Efficacy outcomes

- The efficacy of selpercatinib in treatment-naïve *RET* fusion-positive NSCLC has been demonstrated in LIBRETTO-001, a first in-human, Phase I/II, single arm, open-label trial. Data presented in this submission are from the 15th June 2021 data cut-off.
- The primary endpoint of LIBRETTO-001 was overall response rate (ORR), defined as the proportion of patients with a best overall response (BOR) of either a confirmed complete response (CR) or partial response (PR) based on RECIST v1.1 and Independent Review Committee (IRC) assessment. The ORR in treatment-naïve *RET* fusion-positive NSCLC patients was 84.1% (58/69, 95% CI: 73.3–91.8).[78]
- Key secondary outcomes assessed during LIBRETTO-001 included duration of response (DOR), progression-free survival (PFS) and overall survival (OS) by IRC assessment. In treatment-naïve *RET* fusion-positive NSCLC patients:[78]
  - The median DOR was 20.2 months (95% CI: 13.0–not estimable [NE]), with progressed disease (PD) observed in [redacted] patients in a median follow-up of 20.27 months.[78]
  - The median PFS by IRC assessment was 21.95 months (95% CI: 13.8–NE), with death or disease progression reported in 29/69 (42.0%) patients in a median follow-up of 21.9 months.[77, 78]
  - The median OS was not estimable ([redacted]) at the 15th June 2021 data cut-off, with the majority of patients (49; 71%) remaining alive at a median follow-up of 25.2 months.[77, 78]

Patient reported outcomes

- Patient reported outcomes were assessed using the EORTC QLQ-C30:
  - During treatment, [redacted] of patients experienced meaningful improvements from baseline (of at least 10 points) in the global health status/QoL subscale.
- Overall, at the data cut-off the majority of treatment-naïve advanced *RET* fusion-positive NSCLC patients had improved quality of life as determined by QLQ-C30 subscales during treatment with selpercatinib.

Summary of indirect treatment comparison

- A network meta-analysis (NMA) was performed to compare the efficacy of selpercatinib to other first line treatments relevant to the decision problem for the outcomes of ORR, PFS and OS.
- LIBRETTO-001 was a single-arm trial and therefore did not compare the efficacy of selpercatinib in advanced *RET* fusion-positive NSCLC directly to comparators relevant to the decision problem.
- In order to connect the first line selpercatinib treatment arm of LIBRETTO-001 to the NMA, it was therefore necessary to generate a pseudo-control arm. This was achieved through use of individual patient data from the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial.
- The two treatment arms underwent propensity score matching to account for any differences between trial populations, and the treatment effect estimate between selpercatinib and the pseudo-control arm was integrated into the NMA.

Indirect treatment comparison results

- Treatment with both selpercatinib (OR [95% CrI]: [redacted]) and pembrolizumab combination therapy (OR [95% CrI]: [redacted]) resulted in a [redacted] odds of ORR when compared to pemetrexed plus platinum based chemotherapy.
- In addition, treatment with both selpercatinib (HR [95% CrI]: [redacted]) and pembrolizumab combination therapy (HR [95% CrI]: [redacted]) had a lower hazard of progression or death (PFS) compared to pemetrexed plus platinum based chemotherapy.

- Similarly to PFS, treatment with both selpercatinib (HR [95% CrI]: [redacted]) and pembrolizumab combination therapy (HR [95% CrI]: [redacted]) demonstrated a [redacted] risk of death (OS) when compared to pemetrexed plus platinum based chemotherapy.

Summary of adverse events

- The safety of selpercatinib was assessed in all patients enrolled in LIBRETTO-001 (OSAS) (regardless of tumour type or treatment history) and patients with documented *RET* fusion-positive NSCLC (SAS) trial population.
  - In the OSAS, Grade 3 or 4 TEAEs were reported in 572 (71.9%) patients and 263 (73.9%) patients in the (SAS), irrespective of relatedness to selpercatinib. Common TEAEs were easily monitored and reversible through dose interruption or addressed through dose reduction or concomitant medication.[77]
- Overall, selpercatinib was shown to be well tolerated across patient populations and, considering the clinical efficacy demonstrated in *RET* fusion-positive NSCLC patients, selpercatinib has demonstrated a positive risk: benefit ratio in this population.

Interpretation and conclusions

- Clinical effectiveness and safety evidence from LIBRETTO-001 demonstrates that treatment with selpercatinib provides a clinically meaningful benefit to patients with treatment-naïve advanced *RET* fusion-positive NSCLC, and is well-tolerated.
- Compared to comparators applicable to the decision problem, indirect treatment comparisons demonstrate that selpercatinib is associated with greatest odds of a response and the lowest risk of progression or death.
- The high rates and durability of responses to selpercatinib treatment observed in LIBRETTO-001, which are likely to translate into improved survival, paired with self-reported improvements in patients' HRQoL, support the case for the use in treatment-naïve patients with *RET* fusion-positive NSCLC who require systemic therapy in NHS clinical practice.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant clinical evidence on the efficacy and safety of treatments for advanced *RET* fusion-positive NSCLC who require systemic therapy, including treatment-naïve adults. The original SLR was conducted in January 2016, and subsequently underwent four updates in June 2018, July 2020, July 2021 and April 2022.

Following de-duplication of results, a total of 15,819 publications were screened at the title and abstract stage, of which 887 publications were reviewed at the full-text stage. After exclusion of publications not meeting the eligibility criteria, 163 publications (reporting on 88 unique studies) were included in the SLR. Out of the 163 included publications, a total of 66 first-line to progression studies were identified and ultimately included in the clinical SLR. First-line to progression studies were deemed to most closely match the submission decision problem (see Appendix D.1.1). A full list of the 66 included first-line to progression studies are presented in Appendix D.2. A risk of bias assessment was conducted on all included studies to standards recommended by NICE.[79]

B.2.2 List of relevant clinical effectiveness evidence

The clinical effectiveness of selpercatinib in *RET* fusion-positive NSCLC was assessed in LIBRETTO-001, an ongoing multi-centre, open-label, single-arm, Phase I/II trial. Phase I was designed to understand the pharmacokinetics (PK), safety and maximum tolerated dose (MTD) of selpercatinib, whilst Phase II was designed to perform a preliminary assessment of the efficacy and safety of selpercatinib in patients with *RET*-altered solid tumours. The study

commenced in May 2017 and is the first in-human Phase I/II study for selpercatinib. An overview of LIBRETTO-001 is included in Table 4.

The eligibility criteria for the LIBRETTO-001 trial were broader than the population of relevance for this submission, including patients ≥12 years old with locally advanced or metastatic solid tumours. A subset of patients in the trial are consistent with the population of relevance for this submission: 'treatment-naïve patients with advanced *RET* fusion-positive NSCLC who require systemic therapy'.

Table 4: Clinical effectiveness evidence

Study	**LIBRETTO-001/LOXO-RET 17001 (NCT03157128)[13]**		
Study design	LIBRETTO-001 is a multicentre, open-label, single-arm, Phase I/II study that is ongoing. The trial is demarcated into two parts: Phase I (dose escalation) and Phase II (dose expansion).		
Population	Patients ≥12 years old with locally advanced or metastatic solid tumours, including *RET* fusion-positive solid tumours (e.g. NSCLC, thyroid, pancreas or colorectal), *RET*-mutant medullary thyroid cancer (MTC) and other tumours with RET activation, who progressed on or were intolerant to standard therapy, or no standard therapy exists, or in the opinion of the Investigator were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or declined standard therapy and have an Eastern Cooperative Oncology Group (ECOG) score ≤2 or a Lansky Performance Score (LPS) ≥40%. As of 15th June 2021, N = 796 patients had been enrolled onto the trial, of which N = 356 were *RET* fusion-positive NSCLC patients, N = 69 were treatment-naïve patients (SAS1 population). **Treatment-naïve *RET* fusion-positive NSCLC patients are the focus of this submission.**		
Intervention(s)	Selpercatinib, once or twice daily, depending on the dose level assignment. A recommended Phase II dose of 160 mg BID was selected during Phase I of the study.		
Comparator(s)	N/A – LIBRETTO-001 is a single am trial		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use in the model	LIBRETTO-001 is the first trial demonstrating the efficacy, safety and tolerability of selpercatinib in patients with treatment-naïve *RET*-fusion positive NSCLC.		
Reported outcomes specified in the decision problem	Measures of disease severity and symptom control: • ORR • PFS • OS HRQoL: • EORTC QLQ-C30 Safety outcomes: • AEs		

All other reported outcomes	DOR

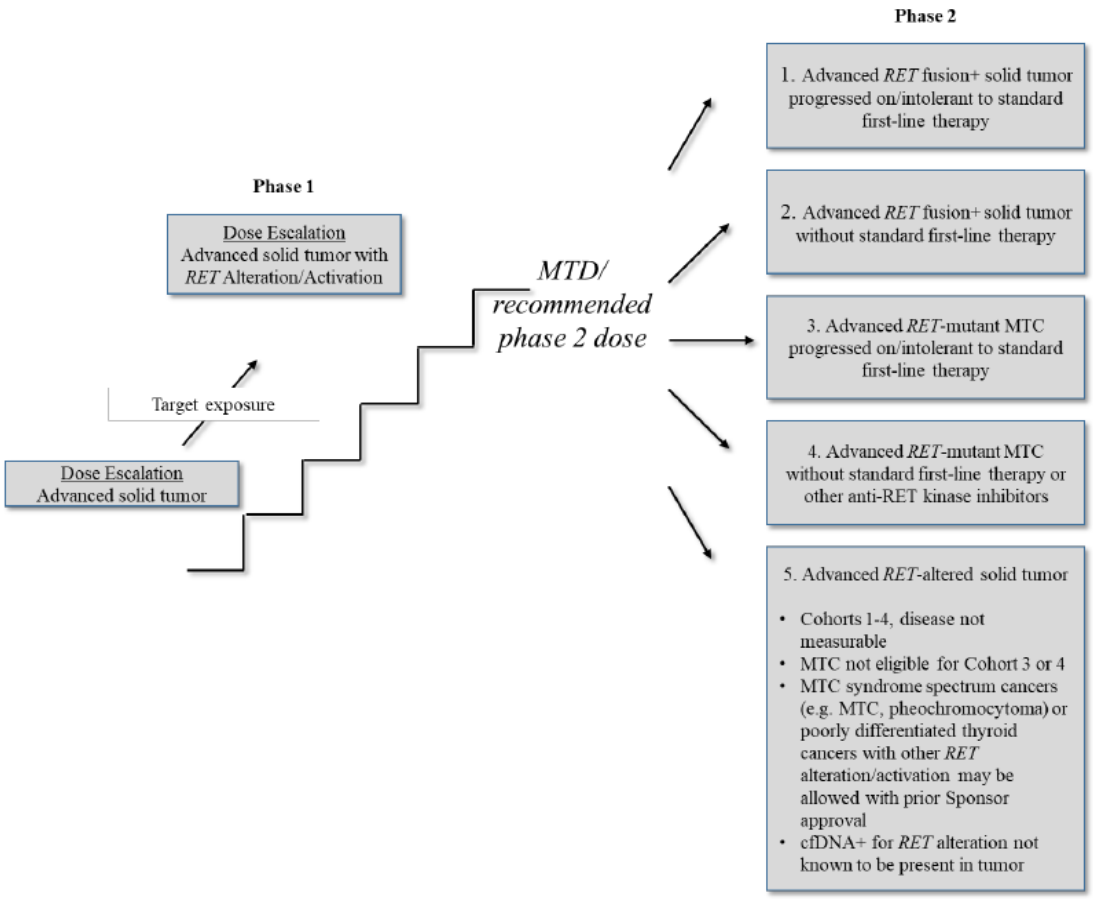
Abbreviations: AEs: adverse events; BID: twice daily; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questions C-30; HRQoL: health-related quality of life; LPS: Lansky Performance Score; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progression free survival; *RET:* rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off),[80] Drilon et al. 2020a.[64]

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

B.2.3.1 Trial design

LIBRETTO-001 is an ongoing multi-centre, open-label, single-arm, Phase I/II study in patients with advanced solid tumours, including *RET* fusion-positive NSCLC tumours.[64] The patient population includes patients >12 years of age with a locally advanced or metastatic solid tumour, who progressed on or were intolerant to standard therapy, or no standard therapy exists, or were not candidates for, or would be unlikely to tolerate or derive significant clinical benefit from, standard therapy or declined standard therapy. Patients were screened for eligibility based on the criteria presented in Table 6, Section B.2.3.2.

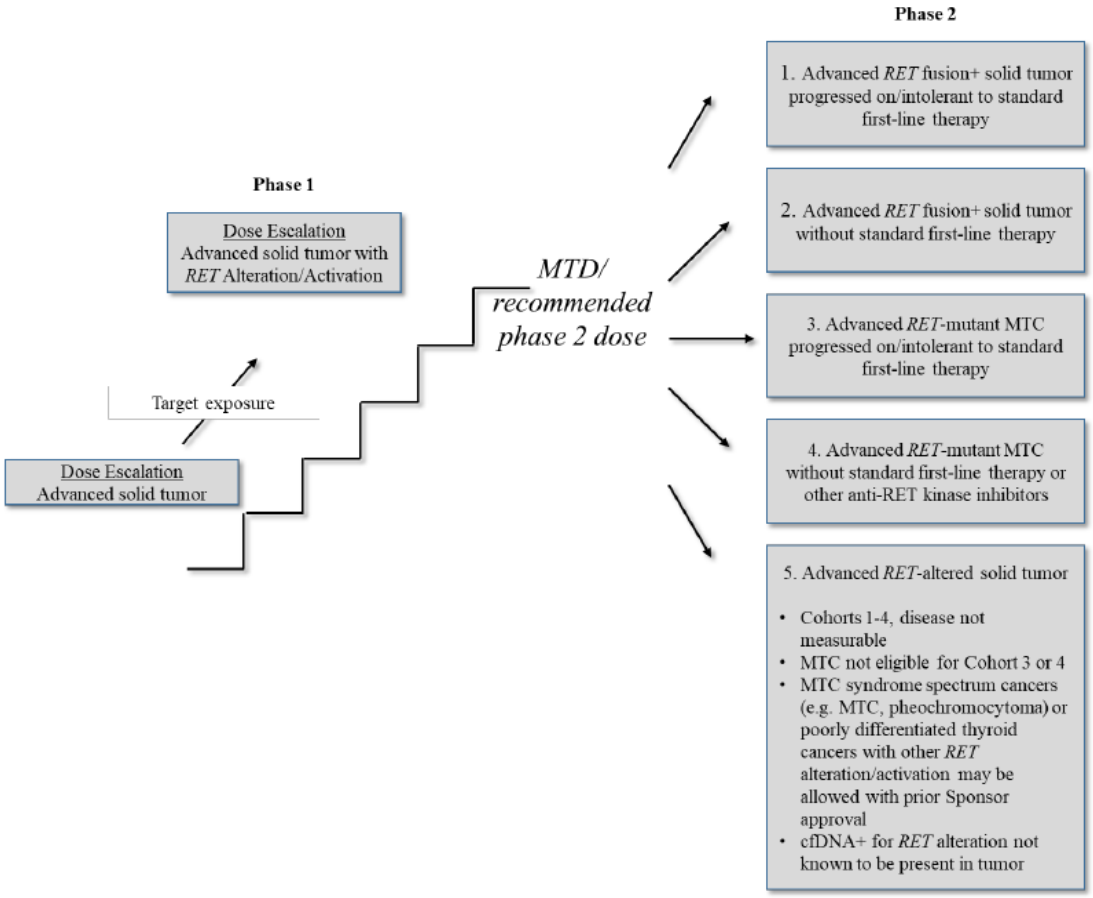
The study includes two phases: Phase I (dose escalation) in which patients were not selected based on *RET* alteration and Phase II (dose expansion), in which five cohorts of patients harbouring *RET* alterations were defined and in which the efficacy and safety of selpercatinib was assessed. The study is currently in Phase II.[81] A schematic of the trial is presented in Figure



3 .

The most recent data cut-off for the interim analysis is 15th June 2021.

Figure 3: Study schematic of the LIBRETTO-001 trial



Abbreviations: MTC: medullary thyroid cancer; MTD: maximum tolerated dose; cfDNA: cell free DNA; *RET*: rearranged during transfection.
Source: Drilon et al. 2020b.[64]

The primary objective of Phase I was to determine the MTD and the recommended Phase II dose (RP2D). Based on results from Phase I escalation phase, the safety review committee (SRC) selected an RP2D of 160 mg.[62]

Patients were subsequently enrolled into one of five Phase II cohorts to better characterise the safety and efficacy of selpercatinib in patients with specific abnormalities in *RET*. Classification into cohorts was based on tumour type, type of *RET* alteration and prior treatment (Table 5).

Table 5: LIBRETTO-001 patient cohorts

Patient cohort	Description
Cohort 1	*RET* fusion-positive solid tumour progressed on or intolerant to ≥1 prior standard first-line therapy, including *RET* fusion-positive NSCLC.
Cohort 2	*RET* fusion-positive solid tumour without prior standard first-line therapy, **including treatment-naïve *RET* fusion-positive NSCLC.**
Cohort 3	*RET*-mutant MTC progressed on or intolerant to ≥1 prior standard first line cabozantinib and/or vandetanib.
Cohort 4	*RET*-mutant MTC without prior standard first line cabozantinib or vandetanib or other kinase inhibitors with anti-*RET* activity.

Cohort 5	Included patients from Cohorts 1 through 4 without measurable disease, MTC patients not meeting the requirements for Cohorts 3 or 4, MTC syndrome spectrum cancers or poorly differentiated thyroid cancers with other *RET* alteration/activation that could be allowed with prior Sponsor approval, cell-free DNA positive for a *RET* gene alteration not known to be present in a tumour sample.
Cohort 6	Patients otherwise eligible for Cohort 1–5 but who discontinued another selective *RET* inhibitor(s) due to intolerance are eligible with prior Sponsor approval.

Abbreviations: DNA: deoxyribonucleic acid; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection.
Source: Drilon et al. 2020b.[64]

For Cohorts 1 to 4, evidence of a *RET* gene alteration in the tumour was required. *RET* fusion-positive NSCLC patients were enrolled into Cohorts 1 and 2 (Table 5), with treatment-naïve patients included in Cohort 2.

Individual patients continued selpercatinib dosing in 28-day cycles until PD, unacceptable toxicity or other reasons for treatment discontinuation.[62] The primary endpoint for the Phase II portion of the trial was ORR using RECIST v1.1. Secondary endpoints included DOR, PFS and OS, whilst the safety, tolerability and PK properties of selpercatinib were also considered.

In line with the decision problem for this submission, only results for the clinical effectiveness of selpercatinib in treatment-naïve patients with *RET* fusion-positive NSCLC will be reported in this submission.

B.2.3.2 Trial methodology

Eligibility criteria

A summary of the methodology and trial design of LIBRETTO-001 is presented in Table 6 below.

Table 6: Summary of LIBRETTO-001 trial methodology

Trial name	**LIBRETTO-001**
Location	A total of 85 investigational study sites across 16 countries worldwide have participated to date: United Kingdom, Canada, United States, Australia, Hong Kong, Japan, South Korea, Singapore, Taiwan, Switzerland, Germany, Denmark, Spain, France, Italy, Israel.
Trial design	A multicentre, open-label, single-arm, Phase I/II study in patients with advanced solid tumours, including RET-alterations.
Eligibility criteria for participants	**Inclusion criteria:** • At least 18 years of age (for countries and sites where approved, patients as young as 12 years of age could be enrolled). • Patients with a locally advanced or metastatic solid tumour who progressed on or were intolerant to standard therapy, or no standard therapy exists, or were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or declined standard therapy. • For patients enrolled into the Phase II dose expansion portion of the study, evidence of a RET gene alteration in the tumour (i.e. not just blood), was required. • ECOG performance status of 0, 1, or 2 (age ≥16 years) or LPS ≥40% (age <16 years) with no sudden deterioration two weeks prior to the first dose of study treatment. **Exclusion criteria:** • Phase II Cohorts 1 through 4: an additional validated oncogenic driver that could cause resistance to selpercatinib treatment. • Major surgery (excluding placement of vascular access) within four weeks prior to planned start of selpercatinib • Radiotherapy with a limited field of radiation for palliation within one week of the first dose of study treatment (with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least four weeks prior to the first dose of study treatment). • Any unresolved toxicities from prior therapy greater than National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy. • Symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis or untreated spinal cord compression (unless neurological symptoms and CNS imagine are stable and steroid dose is stable for 14 days prior to first dose of selpercatinib and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery). • Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of selpercatinib or prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) >470 msec on at least 2/3 consecutive echocardiograms (ECGs) and mean QTcF >470 msec on all 3 ECGs during screening.

	• Active uncontrolled systemic bacterial, viral or fungal infection or clinically significant, active disease process, which in the opinion of the Investigator makes the risk: benefit unfavourable for the patient to participate in the trial. Screening for chronic conditions is not required. • Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug. • Uncontrolled symptomatic hyperthyroidism or hypothyroidism • Uncontrolled symptomatic hypercalcaemia or hypocalcaemia • Pregnancy or lactation • Active second malignancy other than minor treatment of indolent cancers
Method of study drug administration	Selpercatinib was administered in oral form. A RP2D of 160 mg BID was selected for Phase II based on results from Phase I of the study.
Permitted and disallowed concomitant medication	**Permitted:** • Standard supportive medications used in accordance with institutional guidelines and Investigator discretion: • Haematopoietic growth factors to treat neutropoenia, anaemia, or thrombocytopaenia in accordance with American Society of Clinical Oncology (ASCO) guidelines (but not for prophylaxis in Cycle 1) • Red blood cell (RBC) and platelet transfusions • Anti-emetic, analgesic and antidiarrheal medications • Electrolyte repletion (e.g. calcium and magnesium) to correct low electrolyte levels • Glucocorticoids (approximately 10 mg per day prednisone or equivalent, unless there was a compelling clinical rationale for a higher dose articulated by the Investigator and approved by the Sponsor), including short courses to treat asthma, chronic obstructive pulmonary disease, etc. • Thyroid replacement therapy for hypothyroidism • Bisphosphonates, denosumab and other medications for the treatment of osteoporosis, prevention of skeletal-related events from bone metastases and/or hypoparathyroidism. • Hormonal therapy for patients with prostate cancer (e.g. gonadotropin-releasing hormone or luteinizing hormone-releasing hormone agonists) and breast cancer (e.g. aromatase inhibitors, selective estrogenic receptor modulators or degraders), that the patient was on for the previous 28 days. **Disallowed:** • Prior treatment with a selective RET inhibitor(s) • Concomitant systemic anti-cancer agents • Haematopoietic growth factors for prophylaxis in Cycle 1 • Therapeutic monoclonal antibodies • Drugs with immunosuppressant properties • Medications known to be strong inhibitors or inducers of CYP3A4 (moderate inhibitors/inducers could be taken with caution. If patients received strong CYP3A4 inhibitors/inducers, then the Sponsor was consulted to determine whether to stop selpercatinib or remove the patient from the study).

	• Herbal products, such as St John's wort, which could decrease the drug levels of selpercatinib • Investigational agents (other than selpercatinib) • No new, alternative systemic anticancer therapy was allowed prior to documentation of progressive disease • The concomitant use of proton pump inhibitors (PPIs) was prohibited, and patients were to discontinue PPIs one or more weeks prior to the first dose of selpercatinib • Histamine type-2 blocking agents were required be administered only between two and three hours after the dose of selpercatinib • Antacids e.g. aluminium hydroxide/magnesium hydroxide/simethicone or calcium carbonate, if necessary, were required to be administered two or more hours before and/or after selpercatinib.
Primary outcome	**Phase I:** • Identification of the MTD and the RP2D of selpercatinib for further clinical investigation **Phase II:** • The primary endpoint was ORR based on RECIST v1.1 or RANO, as appropriate to the tumour type as assessed by IRC
Secondary and exploratory outcomes	**Secondary endpoints:** • Phase I: determination of the safety and tolerability of selpercatinib, characterisation of the PK properties and assessment of the anti-tumour activity of selpercatinib by determining ORR using RECIST v1.1 or RANO • Phase II: BOR, DOR, clinical benefit rate (CBR), CNS ORR, CNS DOR, PFS, OS, AEs and changes from baseline in clinical safety laboratory values and vital signs, characterisation of PK properties **Exploratory endpoints:** • Determination of the relationship between pharmacokinetics and drug effects (including efficacy and safety) • Evaluation of serum tumour markers • Characterisation of RET gene fusions and mutations and concurrently activated oncogenic pathways by molecular assays, including NGS from tumour biopsies and cell free DNA (cfDNA) • Collection of PROs data to explore disease-related symptoms and health related quality of life (HRQoL)
Pre-planned subgroups	The primary objective was analysed by several demographic variables for NSCLC patients enrolled in the trial: • Age (≥65 versus <65) • Sex (male versus female) • Race (white versus other) • ECOG (0 versus 1–2) • Metastatic disease (yes versus no) • CNS metastasis at baseline by investigator (yes versus no) The primary objective was also analysed by type of *RET* fusion partner and type of *RET* molecular assay used for NSCLC patients enrolled in the trial: • Fusion partner:

	• KIF5B • CCDC6 • NCOA4 • KIAA1468 • ARHGAP12 • CCDC88C • CLIP1 • PRKAR1A • RBPM and DOCK 1 • TRIM24 • Other • Unknown • Molecular assay: • NGS on blood or plasma • NGS on tumour • PCR • Other
Duration of study and follow-up	The study is ongoing. The first patient was treated on 9th May 2017. At the latest data cut-off of 15th June 2021, the median follow-up was 25.2 months for OS and 21.9 months for PFS for SAS1 (treatment-naïve) patients.[77] Patients continued selpercatinib dosing in 28-day cycles until PD, unacceptable toxicity or other reasons for treatment discontinuation. Four weeks (28 days + 7 days) after the last dose of study drug, all treated patients underwent a safety follow-up (SFU) assessment. All patients were also to undergo long term follow-up (LTFU) assessments every 3 months.

Abbreviations: ACTH: adrenocorticotropic hormone; AE: adverse event; ASCO: American Society for Clinical Oncology; BID: twice daily; BOR: best overall response; CBR: clinical benefit rate; CEA: carcinoembryonic antigen; cfDNA: circulating free DNA; CNS: central nervous system; CYP3A4: cytochrome P450 3A4; DOR: duration of response; ECGs: electrocardiograms; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HRQoL: health related quality of life; IRC: independent review committee; LPS: Lansky Performance Score; LTFU: long term follow-up; MTC: medullary thyroid cancer; NGS: next generation sequencing; NCI CTCAE: National Cancer Institute Common Terminology for Adverse Events; ORR: objective response rate; OS: overall survival; PCR: polymerase chain reaction; PD: progressive disease; PD-L1: programmed death ligand 1; PFS: progression free survival; PPI: proton pump inhibitors; PRO: patient reported outcome; QD: once daily; QTcF: QT interval corrected for heart rate using Fridericia's formula; RANO: Response assessment in neuro-oncology criteria; RBC: red blood cell; RECIST: response evaluation criteria in solid tumours; *RET*: rearranged during transfection; RP2D: recommended Phase II dose; SAS1: Supplemental Analysis Set 1; SFU: safety follow-up.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off);.[80] Drilon *et al.* 2020a.[65] Drilon et al. 2022.[77]

B.2.3.3 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Analysis sets

There were 5 analysis sets in LIBRETTO-001 for patients with NSCLC (Figure 4 and Table 7). In line with the decision problem, only clinical effectiveness data from treatment-naïve patients with measurable disease are considered in this submission. These patients comprised the Supplemental Analysis Set 1 (SAS1).

Figure 4: Enrolment and derivation of analysis sets in LIBRETTO-001

Abbreviations: BID: twice daily; MTC: medullary thyroid cancer; N: number of patients; NSCLC: non-small cell lung cancer; QD: once daily; RET: Rearranged during Transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80]

Table 7: LIBRETTO-001 analysis set definitions

Analysis set	Analysis set description	Number of patients
Efficacy analysis (NSCLC)		
Primary Analysis Set (second line)	The first 105 *RET* fusion-positive NSCLC patients enrolled in Phase I and Phase II who met the following criteria: 1. Evidence of a protocol-defined qualifying and definitive RET fusion, prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a RET fusion co-occurring with another putative oncogenic driver, as determined at the time of study enrolment by local testing, were included 2. Measurable disease by RECIST v1.1 by IA[a] 3. Received 1 or more lines of prior platinum-based chemotherapy 4. Received 1 or more doses of selpercatinib	105

Analysis set	Analysis set description		Number of patients
Efficacy analysis (NSCLC)			
Integrated Analysis Set (second line)	All *RET* fusion-positive NSCLC patients treated in LIBRETTO-001 by the data cut-off date who met PAS criteria 1–4. Included all PAS patients and those enrolled after the 105th patient but on or before the data cut-off.		247
Supplemental Analysis Sets	• All other *RET* fusion-positive NSCLC patients (e.g. not part of the PAS/IAS) who were treated in LIBRETTO-001 as of the data cut-off date • SAS1 and SAS2: met PAS criteria 1, 2 and 4 • SAS3: met PAS criteria 1 and 4 • SAS assignment was non-overlapping; thus SAS1–3 are mutually exclusive with each other.	**SAS1 (treatment-naïve; population of interest to this submission):** • No prior systemic therapy	**69**
		SAS2 (prior other systemic therapy): • Received prior systemic therapy other than platinum-based chemotherapy	[redacted]
		SAS3 (non-measurable disease): • No measurable disease[b]	[redacted]
Safety analysis			
Overall Safety Analysis Set	Patients treated with selpercatinib as of a data cut-off of 15th June 2021.	**NSCLC Safety Analysis Set:** *RET* fusion-positive NSCLC	356
		RET-mutant MTC	[redacted]
		RET fusion-positive thyroid cancers	[redacted]
		RET fusion-positive other cancers	[redacted]
		Other cancers	[redacted]
		Total	796

Footnotes: [a]Patients without measurable disease who were enrolled in Phase I dose escalation were included in the PAS; [b]Patients without measurable disease who were enrolled into Phase I dose expansion Cohort 5 (per protocol version 4.0 or earlier) or Phase 2 Cohort 5 (per protocol version 5.0 and later).
Abbreviations: CLIA: Clinical Laboratory Improvement Amendments; IA: Investigator Assessment; IAS: Integrated Analysis Set; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; PAS: Primary Analysis Set; RECIST v1.1: Response Evaluation Criteria in Solid Tumours, Version 1.1; *RET*: rearranged during transfection; SAS: Supplemental Analysis Set; SAS1: Supplemental Analysis Set 1; SAS2: Supplemental Analysis Set 2; SAS3: Supplemental Analysis Set 3; SCE: Summary of Clinical Efficacy; US: United States.
Source Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off),[80] Drilon et al. 2020b.[64] Drilon et al. 2022.[77]

Summary of clinical data cut-off dates

An interim analysis was conducted for 796 patients with advanced solid tumours who had enrolled in the LIBRETTO-001 trial as of a 15th June 2021 data cut-off. Unless noted otherwise, the results presented and analysed in this submission are based on this data cut-off. The safety evaluable data set includes all 796 patients treated with selpercatinib as of the 15th June 2021 data cut-off.[77]

Statistical methods

Table 8: Statistical methods for the primary analysis of LIBRETTO-001

Trial name	LIBRETTO-001
Hypothesis objective	**Phase I:** • The primary objective of Phase I was to determine the MTD and/or the RP2D of selpercatinib **Phase II:** • The primary objective of Phase II was to assess, for each Phase II expansion cohort, the anti-tumour activity of selpercatinib by determining ORR using RECIST v1.1 or RANO, as appropriate for the tumour type
Statistical analysis	• Efficacy analyses were presented by Phase II cohort. Patients treated during the Phase I portion of the study who meet the Phase II eligibility criteria for one of the Phase II cohorts were included as part of the evaluable patients for that cohort for efficacy analyse. • The analysis of response for the main body of this submission was determined by the IRC, while those assessed by the Investigator are presented in Appendix L. • For the primary endpoint, BOR for each patient (CR, PR, stable disease, PR, or unevaluable) occurring between the first dose of selpercatinib and the date of documented disease progression or the date of subsequent anticancer therapy or cancer-related surgery was determined based on the RECIST v1.1 criteria for primary solid tumours. All objective responses were confirmed by a second scan at least 28 days after the initial response. • Best overall response was summarised descriptively to show the number and percentage of patients in each response category. The estimates of ORR were calculated based on the maximum likelihood estimator (i.e. the crude proportion of patients with best overall response of CR or PR) . • Waterfall plots were used to depict graphically the maximum decrease from baseline in the sum of the diameters of target lesions. • The estimate of the ORR was accompanied by 2-sided 95% exact binomial confidence intervals (CI). • To assess the consistency of ORR across selected subgroups and special populations, prespecified supportive subgroup analyses were performed (see Table 7). These analyses were conducted in all the analysis sets including the SAS1 population.
Sample size, power calculation	**Phase I** • The total number of patients to be enrolled in Phase I depended upon the observed safety profile, which determined the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD/RP2D for further study. If approximately 15 patients were enrolled in each planned dose cohort (Cohorts 1–8), a total of approximately 120 patients would be enrolled in Phase I.

	Phase II • For Cohort 2, the population of relevance for this submission, (patients with *RET* fusion-positive solid tumours without prior standard first line therapy), a true ORR of ≥55% was hypothesised when selpercatinib was administered to such patients. A sample size of 59 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 35%.

Data management, patient withdrawals	Data censoring conditions for DOR, OS and PFS were as described below. If a patient met more than one of these conditions, then the scenario that occurred first was used for the analysis.
	DOR and OS:
	DOR and OS were right censored for patients who met one or more of the following conditions:
	• Subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression
	  ○ Censored at the date of the last evaluable disease assessment prior to start of anticancer therapy or surgery
	• Died or experienced documented disease progression after missing two or more consecutively scheduled disease assessment visits
	  ○ Censored at the date of the last evaluable disease assessment visit without documentation of disease progression before the first missed visit
	• Alive and without documented disease progression on or before the data cut-off date
	  ○ Censored at the date of the last evaluable disease assessment
	PFS:
	• PFS was right censored for patients who met one or more of the following conditions:
	• No post-baseline disease assessments, unless death occurred prior to the first planned assessment (in which case death will be considered a PFS event)
	  ○ Censored at the date of the first dose of selpercatinib
	• Subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression
	  ○ Censored at the date of the last evaluable disease assessment prior to start of anticancer therapy or surgery
	• Died or documented disease progression after missing two or more consecutively scheduled disease assessment visits
	  ○ Censored at the date of the last evaluable disease assessment visit without documentation of disease progression before the first missed visit
	• Alive and without documented disease progression on or before the data cut-off date
	  ○ Censored at the date of the last evaluable disease assessment

Abbreviations: AE: adverse event; BOR: best overall response; CI: confidence interval; CR: complete response; DLT: dose limiting toxicity; DOR: duration of response; IRC: Independent Review Committee; MKI: multi-kinase inhibitor; MTC: medullary thyroid cancer; MTD: maximum tolerated dose; ORR: objective response rate; OS: overall survival; *RET*: rearranged during transfection; PFS: progression-free survival; PK: pharmacokinetic; PR: partial response; RP2D: recommended Phase II dose; SRC: Safety Review Committee.
Source: Drilon et al. 2020b.[64]

Definitions for outcome measures

A variety of outcomes were employed to explore the efficacy of selpercatinib in treatment-naïve patients with *RET* fusion-positive NSCLC. Definitions for these outcome measures are presented in Table 9.

Table 9: Definitions for outcome measures used in LIBRETTO-001

Outcome measure	Definition
Primary outcome	
Objective response rate	ORR was defined as the proportion of patients with BOR of confirmed CR or confirmed PR based on RECIST v1.1. Best overall response was defined as the best response designations for each patient recorded between the date of the first dose of selpercatinib and the data cut-off, or the date of documented disease progression per RECIST v1.1 or the date of subsequent therapy or cancer-related surgery. Definitions of response by RECIST v1.1 are as follows:[82] • **Complete Response (CR)**: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. • **Partial Response (PR)**: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. • **Progressive Disease (PD)**: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).. • **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Secondary outcomes	
Duration of response	DOR was calculated for patients who achieved either a CR or PR. For such patients, DOR was defined as the number of months from the start date of CR or PR (whichever response was observed first) and the first date that recurrent or progressive disease was objectively documented. If a patient died, irrespective of cause, without documentation of recurrent or progressive disease beforehand, then the date of death was used to denote the response end date.
Progression free survival	PFS was defined as the number of months elapsed between the date of the first dose of selpercatinib and the earliest date of documented progressive disease, as per RECIST v1.1 or death (whatever the cause).
Overall survival	OS was defined as the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause).
EORTC QLQ-C30	The EORTC QLQ-C30 is a validated instrument that assesses HRQoL in adult cancer patients. It includes a total of 30 items and is composed of scales that evaluate physical (5 items), emotional (4 items), role (2 items), cognitive (2 items) and social (2 items) functioning, as well as global health status (2 items). Higher mean scores on these scales represent better functioning. There are also 3 symptom scales measuring nausea and vomiting (2 items), fatigue (3 items) and pain (2 items), and 6 single items assessing financial impact and various physical symptoms. Higher mean

	scores on these scales represent better functioning or greater symptomology. EORTC QLQ-C30 subscale scores range from 0 to 100. Descriptive analyses reported median/quartile, mean/standard deviation and mean change/standard error from baseline for each subscale at each study visit. A minimal clinically meaningful difference was defined as at least a 10-point difference from the baseline assessment value for each patient, consistent with published work in oncology.[83] Patients with "improvement" were defined as those who demonstrated a ≥10-point improvement from their baseline score. Patients with "worsening" were defined as those who demonstrated a deterioration by ≥10-points from their baseline score. A sustained change (improvement or worsening) was defined as an improvement or worsening, respectively, (as defined above) without any further change in score ≥10 points.

Abbreviations: BOR: best overall response; CR: complete response; DOR: duration of response; EORTC QLQ: European Organisation for Research and Treatment of Cancer quality of life questionnaire; HRQoL: health-related quality of life; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease.
Source: Drilon et al. 2020b.[64]

B.2.3.4 Baseline characteristics

A summary of patient demographics and other baseline characteristics for the 69 patients in the SAS1 population with *RET* fusion-positive NSCLC enrolled in LIBRETTO-001 is provided below.[77]

The median age of patients with in the SAS1 population was 63 (range: 23–92) years and a greater proportion of participants were female (62.3%; Table 10). The majority (69.6%) of patients were white, with a high proportion of patients identified as Asian (18.8%). Most participants (69.6%) reported never smoking.[77] The younger age, as well as the higher proportion of females, Asian patients and non-smokers is consistent with the patient profile of *RET* fusion-positive NSCLC reported in the literature, and mirrors the real-world patient profile in England.[2, 37]

In the SAS1 population, the median time from diagnosis was [redacted] months ([redacted]; Table 11). Most patients ([redacted]) had metastatic disease at enrolment, with 23.2% exhibiting CNS metastases at baseline. In addition, most patients were diagnosed with Stage IV or greater disease ([redacted]). This was higher than England, where 46.8% of NSCLC patients were diagnosed at Stage IV in 2017.[84] NGS on tumour samples ([redacted]) was the most common method of determining *RET* fusion status, which will mirror English clinical practice following the growing establishment of Genomic Hubs (Table 11).[80]

In line with the population described in the decision problem, no patients in the SAS1 subgroup had received prior systemic therapy or treatment other than cancer surgery ([redacted]) or radiotherapy ([redacted]%; Table 12).

Table 10: Baseline demographic characteristics for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)

Characteristics	SAS1 (treatment-naïve) N = 69
Age, years	
Median (range)	63.0 (23–92)

Age group, n (%)	
18–44 years	[redacted]
45–64 years	[redacted]
65–74 years	[redacted]
75 –84 years	[redacted]
≥85 years	[redacted]
Sex, n (%)	
Male	26 (37.7)
Female	43 (62.3)
Race, n (%)	
White	48 (69.6)
Black	4 (5.8)
Asian	13 (18.8)
Other/Missing	4 (5.8)
Ethnicity, n (%)	
Hispanic or Latino	[redacted]
Not Hispanic or Latino	[redacted]
Missing	[redacted]
Body weight, kg	
Median (range)	[redacted]
Baseline ECOG, n (%)	
0	25 (36.2)
1	40 (58.0)
2	4 (5.8)
Smoking history, n (%)	
Never smoked	48 (69.6)
Former smoker	19 (27.5)
Current smoker	2 (2.9)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; SAS1: Supplemental Analysis Set 1.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Drilon *et al.* 2022.[77]

Table 11: Baseline disease characteristics for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)

Characteristics	SAS1 (treatment-naïve) N = 69
Stage at diagnosis, n (%)	
I, IA, IB	[redacted]
II, IIA, IIB	[redacted]
IIIA, IIIB	[redacted]
IIIC	[redacted]

IV	[redacted]
IVA	[redacted]
IVB	[redacted]
IVC	[redacted]
Missing	[redacted]
Time from diagnosis, months	
Median (range)	[redacted]
History of metastatic disease, n (%)	
Yes	[redacted]
No	[redacted]
Time from diagnosis of metastatic disease, months	
Median	[redacted]
Range	[redacted]
At least 1 measurable lesion by investigator, n (%)	
Yes	[redacted]
No	[redacted]
Sum of diameters at baseline by investigator, mm	
Median (range)	[redacted]
CNS metastases at baseline by investigator, n (%)	
Yes	16 (23.2)
No	53 (76.8)
***RET* fusion partner, n (%)**	
KIF5B	48 (69.6)
CCDC6	10 (14.5)
NCOA4	1 (1.4)
Other	[redacted]
Unknown	[redacted]
Molecular assay type, n (%)	
NGS on tumour	[redacted]
PCR on tumour	[redacted]
NGS on plasma/blood	[redacted]
FISH on tumour	[redacted]
Nanostring technology	[redacted]

Abbreviations: CNS: central nervous system; FISH: fluorescent in situ hybridisation; NGS: next generation sequencing; PCR: polymerase chain reaction; RET: rearranged during transfection; SAS1: Supplemental Analysis Set 1.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Drilon *et al.* 2022.[77]

Table 12: Prior cancer-related treatments for *RET* fusion-positive NSCLC

Characteristics	SAS1 (treatment-naïve)

	N = 69
Prior systemic therapy, n (%)	
Yes	[redacted]
No	[redacted]
Prior radiotherapy, n (%)	
Yes	[redacted]
No	[redacted]
Prior cancer related surgery, n (%)	
Yes	[redacted]
No	[redacted]

Abbreviations: SAS1: Supplemental Analysis Set 1.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Participants Flow

The patient disposition of the SAS1 analysis set is presented in Table 13. Of the 69 patients included, 32 (46.4%) were still on treatment as of the 15th June 2021 data cut-off.[80] For all patients, the most common reason for treatment discontinuation was disease progression [redacted].[80]

Table 13: Patient disposition of *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (15th June 2021 data cut-off)

Characteristics	SAS1 (treatment-naïve) N = 69
Treated	69
Treatment ongoing, n (%)	[redacted] (46.4)
Treatment discontinued, n (%)	[redacted]
Disease progression	[redacted]
Adverse event	[redacted]
Withdrawal of consent	[redacted]
Death	[redacted]
Other	[redacted]
Treatment continued post-progression, n (%)	[redacted]
Study status:	
Continuing study, n (%)	[redacted]
Discontinued study, n (%)	[redacted]
Reason for study discontinuation	
Withdrawal of consent	[redacted]
Death	[redacted]

Abbreviations: SAS1: Supplemental Analysis Set 1.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Drilon *et al.* 2022.[77]

B.2.4 Quality assessment of the relevant clinical effectiveness evidence

The LIBRETTO-001 trial was assessed for risk of bias and generalisability in line with NICE requirements. Overall, the results of the LIBRETTO-001 trial may be considered at low risk of bias, as summarised in Table 14.

Whilst LIBRETTO-001 was single arm in nature, the trial had a clearly focussed issue, the exposure and the outcome were both accurately measured to minimise bias, and the results were considered precise, believable and generalisable to the UK population.

Table 14: Quality assessment of the LIBRETTO-001 trial

Study Question	Grade (yes/no/unclear)
1. Did the study address a clearly focussed issue?	Yes. The population was clearly defined, and the aim of the study was to assess the efficacy, safety, and pharmacokinetics of selpercatinib in patients with advanced solid tumours including *RET* fusion-positive solid tumours. The primary endpoint of Phase I was MTD and/or the RP2D of selpercatinib. The primary endpoint of Phase II was ORR and secondary endpoints include DOR, PFS and OS.
2. Was the cohort recruited in an acceptable way?	Clear inclusion and exclusion criteria are outlined in Drilon et al. 2020b and reported in Table 6.[64] However, it is an open-label, single-arm study, which could create selection bias.
3. Was the exposure accurately measured to minimise bias?	Yes. This was a prospective study with an appropriate study design with validated tools for outcome assessment and data collection. All patients were classified using the same criteria.
4. Was the outcome accurately measured to minimise bias?	Yes. Validated objective measurements were used. Tumour response was measured by RECIST v1.1 and assessed by an IRC. Adverse events were assessed using CTCAE. Neither the patients nor the outcome assessor were blinded as it was an open-label, single-arm study.
5A. Have the authors identified all important confounding factors? List the ones you think might be important, that the author missed.	No. Confounding factors were not listed, however, baseline characteristics are extensively reported (see Section B.2.3.4).
5B. Have they taken account of the confounding factors in the design and/or analysis?	The study has no control arm, therefore randomisation or stratification are not applicable.
6A. Was the follow up of subjects complete enough?	Yes. Out of the 69 subjects enrolled in the treatment-naïve cohort of LIBRETTO-001, a high proportion of patients (46.4%) were continuing treatment at the latest data cut-off.[77]
6B. Was the follow up of subjects long enough?	The follow-up of subjects was long enough to collect a sufficient number of PFS events and estimate the median, however the median OS was not estimable due to a low proportion of events.

7. What are the results of this study?	Selpercatinib was well-tolerated and had marked anti-tumour activity in treatment-naïve *RET* fusion-positive NSCLC patients, as illustrated by the ORR results.
8. How precise are the results?	The results were precise with RECIST assessment used on all scans to determine the ORR with an IRC. Response was confirmed by a repeat assessment no less than 28 days later.
9. Do you believe the results?	Yes. The primary endpoint for Phase II (ORR) aligns with published results from trials for other *RET* selective inhibitors.[85]
10. Can the results be applied to the local population?	Yes. These results can be applied to treatment-naïve patients with *RET*-fusion positive NSCLC.
11. Do the results of this study fit with other available evidence?	Yes. The primary endpoint for Phase II (ORR) was similar to published results from trials for other *RET* selective inhibitors.[85] ORR was 70% in treatment-naïve NSCLC patients treated with pralsetinib in a Phase 1/2 trial compared to 84.1% in the LIBRETTO-001.
12. What are the implications of this study for practice?	The results from this small single-arm study show selpercatinib as a potential effective therapy for NSCLC patients with *RET*-altered tumours in both first- and subsequent lines of therapy.

Abbreviations: CT.gov: clinical trials.gov; CTCAE: common terminology criteria for adverse events; DOR: dose response rate; IRC: Independent Review Committee; MKI: multi-kinase inhibitors; MTC: medullary thyroid cancer; MTD: maximum-tolerated dose; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RECIST: response evaluation criteria in solid tumours; *RET*: rearrangements and/or mutations during transfection.

B.2.5 Clinical effectiveness results of the relevant trials

Summary of clinical effectiveness results

- Selpercatinib treatment resulted in high tumour response rates in the SAS1 trial population (treatment-naïve *RET* fusion-positive NSCLC patients), decreasing tumour size and delaying disease progression for most patients; ORR was 84.1% (58/69, 95% CI: 73.3–91.8)[77]
- DOR was a secondary outcome in LIBRETTO-001. The median DOR was 20.2 months (95% CI: 13.0–not estimable [NE]) in the SAS1 population at the time of data cut-off, with PD observed in [redacted] patients in a median follow-up of 20.27 months[78]
- PFS was a secondary outcome in LIBRETTO-001. The median PFS by IRC assessment was 21.95 months (95% CI: 13.8–NE[redacted] in the SAS1 population[redacted] with death or disease progression reported in 29/69 (42.0%)patients in a median follow-up of 21.9 months[77, 78]
- Progressed disease is associated with reduced patient HRQoL.[6] Results indicate that selpercatinib treatment could bring positive benefits to treatment-naïve *RET* fusion-positive NSCLC patients by delaying disease progression and helping patients to maintain their HRQoL for longer
- OS was considered as a secondary outcome in LIBRETTO-001. The median OS was not estimable ([redacted]) at the 15th June 2021 data cut-off in the SAS1 population, with the majority of patients (49; 71%) remaining alive at a median follow-up of 25.2 months
- Patient reported outcomes were assessed using the EORTC QLQ-C30 in the SAS1 population:
- Patients experienced sustained improvements in QLQ-C30 sub scores: physical (n = [redacted]), emotional (n = [redacted]), role (n = [redacted]) and social function (n = [redacted])
- In general, a higher proportion of NSCLC patients reported improved, rather than worsening, QLQ-C30 scores, with [redacted] versus [redacted] of patients reporting a sustained change of improved versus worsened global health status scores at the 15th June 2021 data cut-off
- The results of LIBRETTO-001 trial demonstrate that treatment with selpercatinib results in a high and durable response rate for treatment-naïve *RET* fusion-positive NSCLC patients, corresponding with maintained benefits to patients' HRQoL and prolonged survival

The clinical effectiveness results in the SAS1 trial population, assessed by IRC, are presented Section B.2.5.1–B.2.5.4 below. Results from the Investigator assessment are available in Appendix L. As of the 15th June 2021 data cut-off, all 69 patients in the SAS1 trial population had at least 6 months follow-up from the first dose of selpercatinib.[80]

B.2.5.1 Primary endpoint: objective response rate

ORR was defined as the proportion of patients with a BOR of confirmed CR or PR based on RECIST v1.1 (see Table 9, Section B.2.3.3). In the SAS1 trial population, the ORR was 84.1% (58/69, 95% CI: 73.3–91.8) as per IRC assessment (Table 15). Based on BOR, 8.7% of patients were assessed to have stable disease, whilst the majority were assessed to have a partial response (78.3%). Only 3 patients (4.3%) were assessed to have progressive disease as BOR.[77]

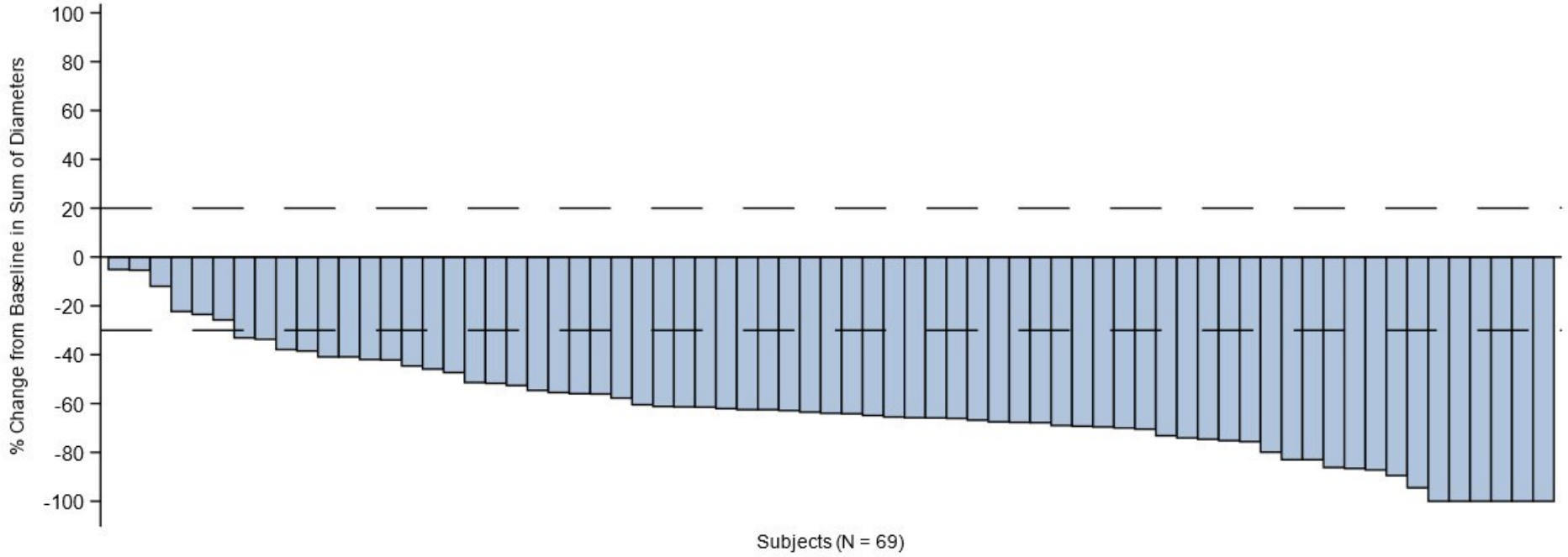
The individual patients' responses to selpercatinib treatment in terms of percentage decrease in tumour size from baseline, as per RECIST v1.1, are illustrated in Figure 5, demonstrating that at the data cut-off, tumour diameter had decreased in all of the 69 patients, decreasing by more than 30% (i.e. at least a partial response was achieved) in all but [redacted] patients.[80] These results indicate that selpercatinib treatment results in high response rates in treatment-naïve *RET* fusion-positive NSCLC patients, delaying disease progression and decreasing tumour size.

Table 15: BOR and ORR for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1; IRC assessment)

Criteria	SAS1 (treatment-naïve) N = 69
Best overall response, n (%)	
Complete response	4 (5.8)
Partial response	54 (78.3)
Stable disease	6 (8.7)
Progressive disease	3 (4.3)
Not evaluable	2 (2.9)
Objective response rate (CR + PR)	
n (%)	58 (84.1)
95% CI	(73.3–91.8)

Abbreviations: CI: confidence intervals; CR: complete response; PR: partial response; SAS1: Supplemental Analysis Set 1.
Sources: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Drilon *et al.* 2022.[77]

Figure 5: Waterfall plot of best change in tumour burden based on IRC assessment for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)



Footnotes: Dotted lines indicate thresholds for partial response and progressive disease. A decrease in tumour size of ≥30% was considered a partial response, whilst an increase in tumour size of ≥20% was considered progressive disease.
Abbreviations: IRC: independent review committee; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; SAS1: Supplemental Analysis Set 1.
Source: Drilon *et al.* 2022.[77]

B.2.5.2 Secondary endpoint: duration of response

For assessment of DOR, time until occurrence of an event was measured. An event was recorded as death or disease progression in a patient. Patients were censored as per the criteria listed in Table 8 (Section B.2.3.3).

Of the 58 patients in the SAS1 trial population who responded to treatment with selpercatinib, at the data cut-off, [redacted] of patients were alive with no documented disease progression. The median DOR by IRC assessment was 20.2 months (95% CI: 13.0–NE) at the time of data cut-off for these patients, with PD observed in [redacted] patients in a median follow-up of 20.27 months (Table 16).[77] As of the 15th June 2021 data cut-off, [redacted] patients had maintained a response for ≥12 months.[80]

By Kaplan-Meier estimate, the probability of remaining in response at 6 months was 87.7% (95% CI: 75.9–93.3) and 66.1% (95% CI: 51.6–77.3) at 12 months.[77] These results indicate that patient benefit from a decrease in tumour size is durable, with almost all patients predicted to maintain their response for 6 months, and over half of patients anticipated to remain in response for at least 12 months. The combination of a high ORR and extended DOR observed with selpercatinib provides a prolonged benefit to patients, translating into stable or improved quality of life (see Section B.2.5.5). The Kaplan-Meier plot of DOR is presented in Figure 6.[80]

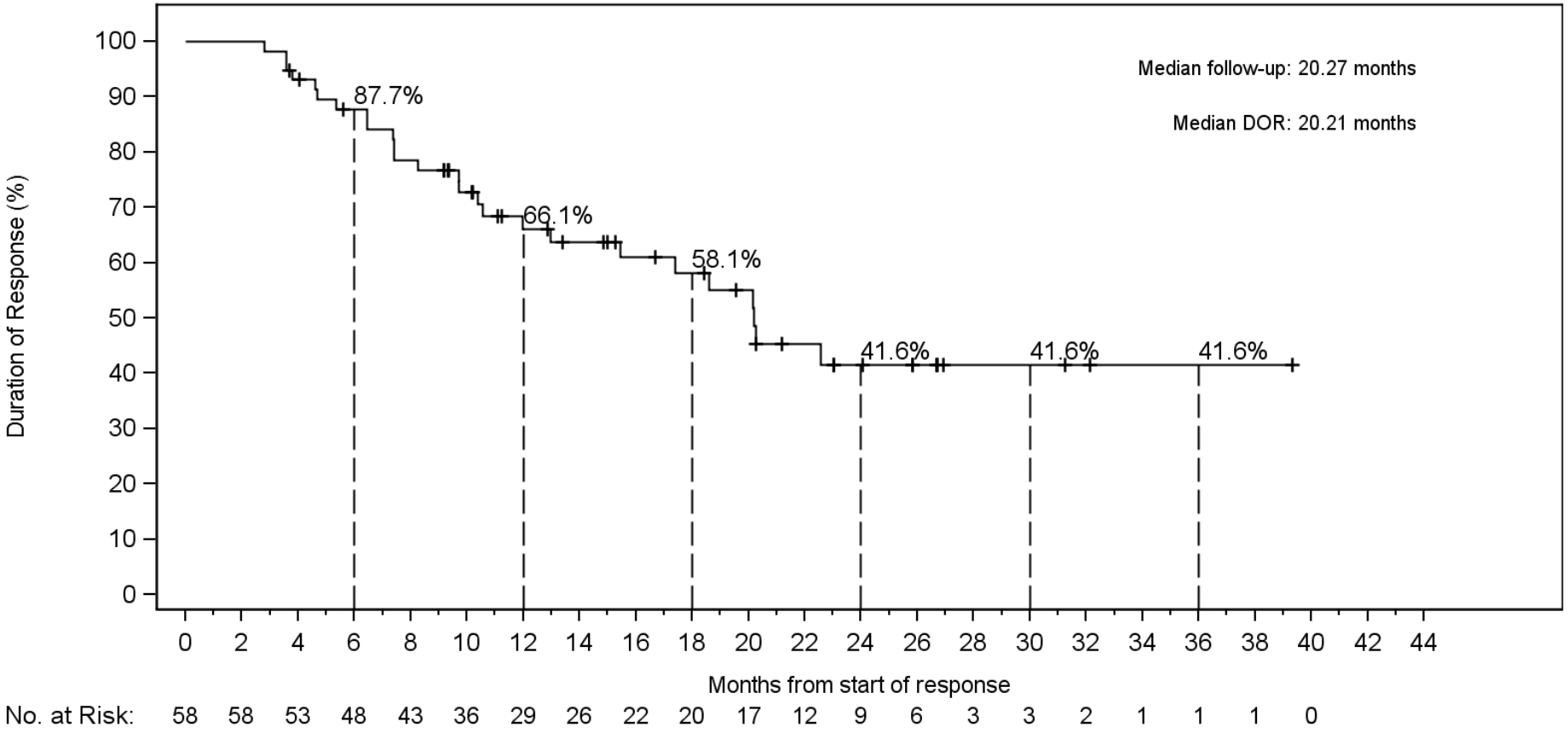
Table 16: DOR for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1; IRC assessment)

Criteria	SAS1 (treatment-naïve) N = 69
Patients with response	58
Response status, n (%)[a]	
Disease progression	[redacted]
Death	[redacted]
Censored	32 (55.2)
Reason censored, n (%)	
Alive without documented disease progression	[redacted]
Subsequent anti-cancer therapy or cancer-related surgery without documented PD	[redacted]
Discontinued from study without documented PD	[redacted]
Discontinued treatment and lost to follow-up	[redacted]
DOR (months)[b,c]	
Median	20.2
95% CI	13.0–NE
Minimum–maximum	[redacted]
Rate (%) of DOR [b, d]	
≥6 months (95% CI)	87.7 (75.9–93.9)
≥12 months (95% CI)	66.1 (51.6–77.3)
≥24 months (95% CI)	41.6 (25.6–56.8)
≥36 months (95% CI)	[redacted]
DOR follow-up (months)[b]	

Median	20.27
25th, 75th percentiles	[redacted]
Observed DOR, n (%)[b]	
<6 months	[redacted]
≥6 to 12 months	[redacted]
≥12 to 18 months	[redacted]
≥18 to 24 months	[redacted]
≥24 months	[redacted]

Footnotes: [a] Satus as of the patient's last disease assessment 15th June 2021.[b]Estimated based on Kaplan-Meier method. [c] 95% CI was calculated using Brookmeyer and Crowley method. [d] 95% Confidence Interval was calculated using Greenwood's formula.
Abbreviations: CI: confidence interval; DOR: duration of response; NE: not evaluable; PD: progressive disease; SAS1: Supplemental Analysis Set 1.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Drilon *et al.* 2022.[77]

Figure 6: Kaplan-Meier plot of DOR based on IRC assessment for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)



Footnotes: Censored patients denoted by "+".
Abbreviations: DOR: duration of response; IRC: independent review committee; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; SAS1: Supplemental Analysis Set 1.
Source: Drilon *et al.* 2022.[77]

B.2.5.3 Secondary endpoint: progression free survival

PFS was derived for each patient as the number of months from the date of the first dose of the study drug until documented disease progression or death due to any cause. Patients were censored as per the criteria listed in Table 8 (Section B.2.3.3).

As of the 15th June 2021 data cut-off, the majority (37; 53.6%) of patients were alive and without documented PD, with a median duration of PFS of 21.95 months (95% CI: 13.8–NE) months.[77] Death or disease progression was reported in 29/69 (42.0%) of patients over a median follow-up of 21.9 months.[78] Due to the majority of patients remaining progression free at the cut-off date, the PFS data are considered immature (Table 17).[80] The majority [redacted] of patients were progression free for ≥12 months, as of the June 2021 data cut-off.[80]

By Kaplan-Meier estimate, the probability of patients being progression-free at 6- and 12- months was [redacted] and 70.6% (95% CI: 57.8–80.2), respectively, by IRC assessment.[77, 80] These results indicate that administration of selpercatinib can produce clinically meaningful responses for a high proportion of treatment-naïve patients, with over two thirds estimated to be event-free (death or disease progression) for at least a year after receiving their first dose. Progressed disease is associated with reduced patient HRQoL, and as such, selpercatinib is likely to bring positive benefits to treatment-naïve *RET* fusion-positive NSCLC patients by delaying disease progression and helping patients to maintain their QoL for longer periods of time.[6] The Kaplan-Meier plot of PFS is presented in Figure 7.[80]

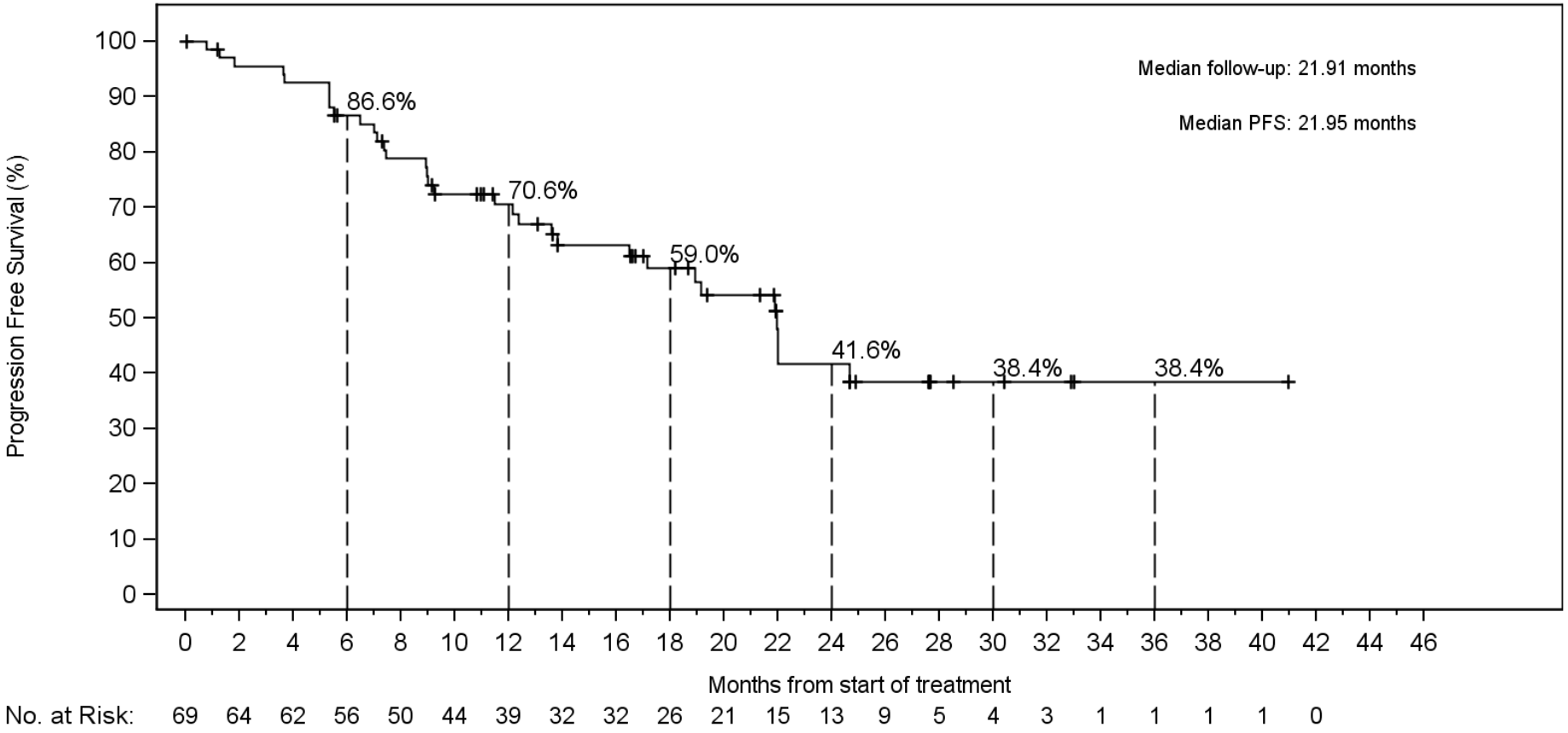
Table 17:PFS for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1; IRC assessment)

Criteria	SAS1 (treatment-naïve) N = 69
Progression status n (%)[a]	
Disease progression	29 (42.0)
Died (no disease progression beforehand)	[redacted]
Censored	37 (53.6)
Reason censored (n, %)	
Alive without documented disease progression	[redacted]
Subsequent anti-cancer therapy or cancer-related surgery without document PD	[redacted]
Discontinued from study without documented PD	[redacted]
Discontinued treatment and lost to follow-up	[redacted]
Duration of PFS (months)[b, c]	
Median	21.95
95% CI	13.8–NE
Minimum–maximum	[redacted]
Rate (%) of PFS[b,d]	
≥6 months (95% CI)	[redacted]
≥12 months (95% CI)	70.6 (57.8–80.2)
≥24 months (95% CI)	41.6 (26.8–55.8)
≥36 months (95% CI)	[redacted]
Duration of PFS follow-up (months)[b]	

Criteria	SAS1 (treatment-naïve) N = 69
Median	21.95
25th, 75th percentiles	[redacted]
Observed PFS, n (%)	
<6 months	13 (18.8)
≥6 to 12 months	17 (24.6)
≥12 to 18 months	13 (18.8)
≥18 to 24 months	13 (18.8)
≥24 months	13 (18.8)

Footnotes: [a] Satus as of the patient's last disease assessment 15th June 2021.[b]Estimated based on Kaplan-Meier method. [c] 95% CI was calculated using Brookmeyer and Crowley method. [d] 95% Confidence Interval was calculated using Greenwood's formula.
Abbreviations: CI: confidence intervals; PD: progressive disease; PFS: progression free survival; NE: not evaluable; SAS1: Supplemental Analysis Set 1.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Drilon *et al.* 2022.[77]

Figure 7: Kaplan-Meier plot of PFS based on IRC assessment for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)



Footnotes: Censored patients denoted by "+".
Abbreviations: IRC: independent review committee; NSCLC: non-small cell lung cancer; PFS: progression free survival; RET: rearranged during transfection; SAS1: Supplemental Analysis Set 1.
Source: Drilon *et al.* 2022.[77]

B.2.5.4 Secondary endpoint: overall survival

For assessment of OS, the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause) was recorded. Patients who were alive or lost to follow-up as of the data cut-off date were right-censored (see detailed censoring criteria listed in Table 8 (Section B.2.3.3). The censoring date was determined from the date the patient was last known to be alive.

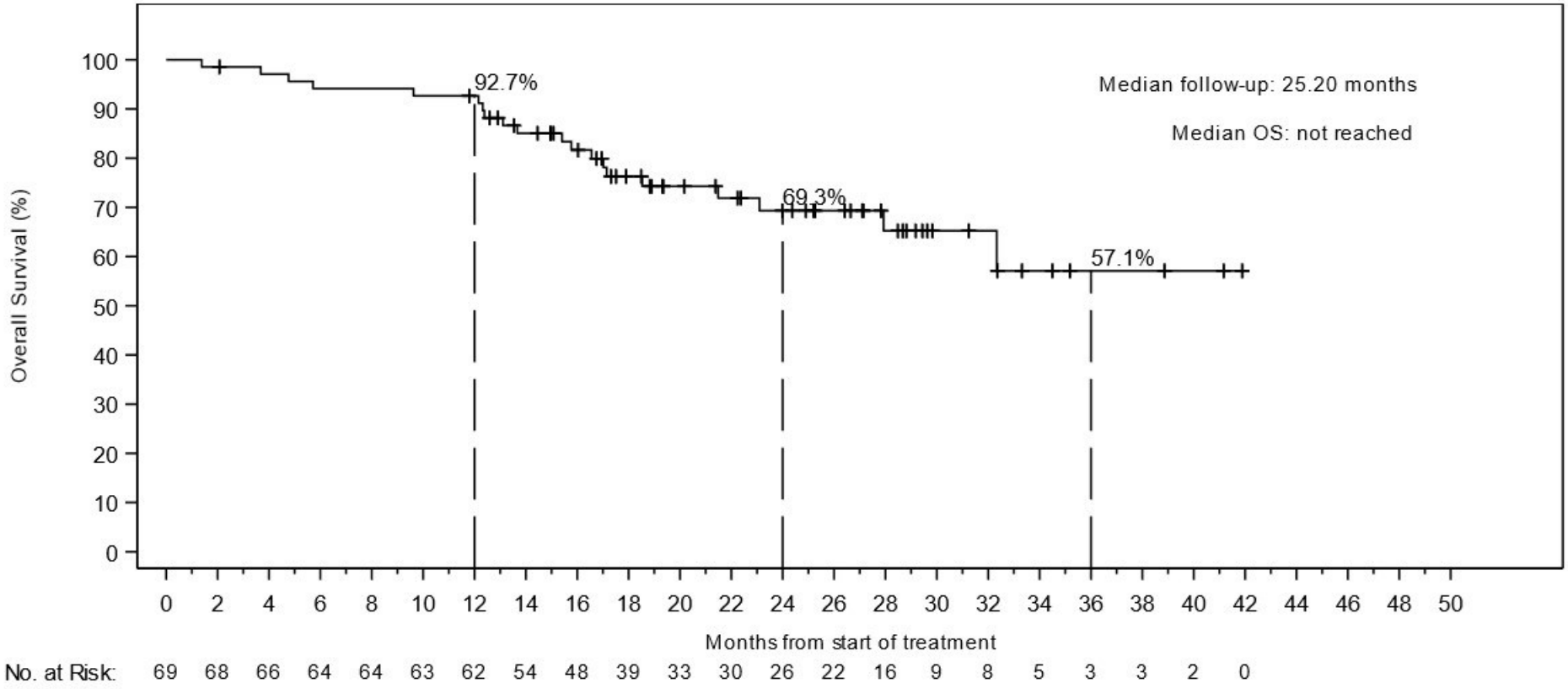
The median OS in the SAS1 trial population was not estimable ([redacted]) at the 15th June 2021 data cut-off, with the majority of patients (49; 71%) remaining alive at a median follow-up of 25.20 months. At 12 months, the OS rate was 92.7% (95% CI: 83.3–96.9) and at 24 months was 69.3% (95% CI: 55.2–79.7), providing preliminary evidence to support that selpercatinib will result in an extension to patients' lives (Table 18).[77, 80] The Kaplan-Meier plot for OS is presented in Figure 8.

Table 18: OS for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)

Criteria	SAS1 (treatment-naïve) N = 69
Survival status n (%)[a]	
Dead	[redacted]
Alive	49 (71.0)
Duration of OS (months)	
Median[b]	[redacted]
95% CI	[redacted]
Minimum–maximum	[redacted]
Rate (%) of OS[b]	
12 months	92.7
95% CI	83.3–96.9
24 months	69.3
95% CI	55.2–79.7
Duration of follow-up (months)[c]	
Median	25.20
25th, 75th percentiles	[redacted]

Footnotes: [a] Satus as of the patient's last disease assessment 15th June 2021. [b] 95% confidence interval was calculated using Greenwood's formula. [c] Estimated based on Kaplan-Meier method.
Abbreviations: CI: confidence intervals; NE: not evaluable; OS: overall survival; SAS1: Supplemental Analysis Set 1.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Drilon *et al.* 2022.[77]

Figure 8: Kaplan-Meier plot of OS for treatment-naïve RET fusion-positive NSCLC (SAS1)



Footnotes: Censored patients denoted by "+".
Abbreviations: IRC: independent review committee; NSCLC: non-small cell lung cancer; OS: overall survival; RET: rearranged during transfection; SAS1: Supplemental Analysis Set 1.
Source: Drilon *et al.* 2022.[77]

B.2.5.5 EORTC QLQ-C30

As of the 15th June 2021 data cut-off, [redacted] patients in the SAS1 trial population had completed a baseline assessment as part of a "QLQ-C30 Analysis Set" and at least one following assessment. EORTC QLQ-C30 questionnaires were administered at baseline and completed approximately every 8 weeks during the first year, at visit 13 and then every 12 weeks until the end of treatment visit, and then at the follow-up visit after treatment discontinuation (see Table 9, Section B.2.3.3 for further details of EORTC QLQ-C30 methodology).[62]

During treatment, [redacted] of patients experienced meaningful improvements (of at least 10 points) in the global health status/QoL subscale. With regards to physical, emotional, role and cognitive function, [redacted], [redacted], [redacted], [redacted] and [redacted] of patients, respectively, reported meaningful improvements during treatment with selpercatinib. Improvements were also seen in the EORTC QLQ-C30 subscales testing symptomology and financial impact of the disease. Of the [redacted] patients who completed the assessments, [redacted] reported an improvement in nausea and vomiting, [redacted] in fatigue, [redacted] in pain, [redacted] in dyspnoea, [redacted] in insomnia, [redacted] in appetite loss, [redacted] in constipation, [redacted] in diarrhoea and [redacted] in financial difficulties.

Across the majority of the QLQ-C30 subscales, a numerically higher proportion of NSCLC patients reported improved scores versus worsening QLQ-C30 subscale scores (Table 19). Overall, at the data cut-off the majority of treatment-naïve advanced *RET* fusion-positive NSCLC patients had improved quality of life as determined by QLQ-C30 subscales during treatment with selpercatinib.

Table 19: EORTC-QLQ-C30: Proportion of patients with *RET* fusion-positive NSCLC who improved or worsened from baseline at scheduled follow-up visits

QLQ-C30 Subscale, n (%)	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11	Cycle 13	Cycle 16	Cycle 19	Cycle 22	Cycle 25	Cycle 28	EoT
Global Health Status/QoL												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Physical Functioning												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Emotional Functioning												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Role Functioning												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Cognitive Functioning												
n	[redacted]											

QLQ-C30 Subscale, n (%)	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11	Cycle 13	Cycle 16	Cycle 19	Cycle 22	Cycle 25	Cycle 28	EoT
Improved	[redacted]											
Worsened	[redacted]											
Social Functioning												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Nausea and Vomiting												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Fatigue												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Pain												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Dyspnea												

QLQ-C30 Subscale, n (%)	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11	Cycle 13	Cycle 16	Cycle 19	Cycle 22	Cycle 25	Cycle 28	EoT
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Insomnia												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Appetite Loss												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Constipation												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Diarrhoea												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											

QLQ-C30 Subscale, n (%)	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11	Cycle 13	Cycle 16	Cycle 19	Cycle 22	Cycle 25	Cycle 28	EoT
Financial Difficulties												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											

Footnotes: Patients who were "improved" were defined as those who demonstrated a ≥10-point change from their baseline score. Patients who "worsened" were defined as those who demonstrated a decrease by ≥10-points from their baseline score.
Abbreviations: EORTC QLQ: European Platform of Cancer Research Quality of Life Questionnaire; EoT: end of treatment; NSCLC: non-small cell lung cancer; QoL: quality of life.

B.2.6 Subgroup analysis

As described in Table 6 (Section B.2.3.3), to assess the consistency of ORR across selected subgroups and special populations, prespecified supportive subgroup analysis based on demographic and baseline characterises was performed on the SAS1 trial population. ORR remained consistent across the prespecified subgroups, demonstrating the efficacy of selpercatinib to be robust to variations in demographics and baseline characteristics (Figure 9 and Figure 10).

In addition, owing to the high prevalence of brain metastases in *RET*-fusion positive NSCLC patients (Table 1) the efficacy of selpercatinib in the subset of patients with brain metastases was investigated. A total of 16 (23.2%) of the 69 treatment-naïve patients had Investigator assessed brain metastases at baseline.[77] Five patients had measurable central nervous system (CNS) disease by IRC and 11 patients had non-measurable CNS disease by IRC. Patients with measurable CNS lesions had a CNS ORR of [redacted]) demonstrating efficacy of selpercatinib against CNS metastases (Table 20).

Figure 9: Forest plots for the subgroup analysis on the ORR based on demographic characteristics (SAS1)

Note: Two-sided 95% exact binomial CI is calculated using the Clopper-Pearson method. Dashed reference line is set at 30%. Solid reference line is set at 84.1% (overall ORR). Higher ORR values correspond to more favourable response outcomes to selpercatinib in the specified subgroup.
Abbreviations: CI: confidence interval; ORR: objective response rate; *RET*: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80]

Figure 10: Forest plots for the subgroup analysis on the ORR based on baseline disease characteristics (SAS1)

Note: Two-sided 95% exact binomial CI is calculated using the Clopper-Pearson method. Dashed reference line is set at 30%. Solid reference line is set at 84.1% (overall ORR). Higher ORR values correspond to more favourable response outcomes to selpercatinib in the specified subgroup.
Abbreviations: CI: confidence interval; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; FISH: fluorescence *in situ* hybridization; NGS: next generation sequencing; ORR: objective response rate; PCR: polymerase chain reaction; PD-1: programmed cell death 1 receptor; PD-L1: programmed cell death receptor ligand 1; *RET*: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80]

Table 20: CNS ORR and DOR by IRC assessment- *RET* fusion-positive treatment-naïve patients with measurable CNS lesions

	NSCLC with Prior RT			No Prior Brain RT (N=3)	All NSCLC (SAS1) (N=5)
	Brain RT ≤2 Months Prior to First Dose (N=2)	Brain RT >2 Months Prior to First Dose (N=0)	All NSCLC with Prior RT (N=2)		
CNS Objective Response Rate[a] (CR + PR)					
Number of Patients with CR + PR (n, %)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
95% CI[b]	[redacted]	N/A	[redacted]	[redacted]	[redacted]
CNS Clinical Benefit Rate					
Number of Patients with CR + PR + SD[c] (n, %)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
95% CI[b]	[redacted]	N/A	[redacted]	[redacted]	[redacted]
CNS Duration of Response (months)[d,e]					
No. of patients censored, n (%)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	N/A	[redacted]	[redacted]	[redacted]

Footnotes: [a]CNS ORR is defined as the proportion of patients with best overall response of CR or PR. Response was confirmed by a repeat assessment no less than 28 days.
[b]95% CI was calculated using Clopper-Pearson method. [c]Indicates SD lasting ≥ 16 weeks following initiation of selpercatinib until the criteria for disease progression was first met. [d]Estimate based on Kaplan-Meier method. +Censored observation.
Abbreviations: CI:confidence interval; CNS: central nervous system; CR: complete response; DOR: duration of response; IRC: Independent Review Committee; N: number of patients; n: number of patients in specific category; NE: not estimable; No: number; NR: not reported; NSCLC: non-small cell lung cancer; ORR: objective response rate; PR: partial response; RET: REarranged during Transfection; RT: radiation therapy.

B.2.7 Meta-analysis

A meta-analysis is a common statistical method used to generate aggregate measures of effect from individual trials. As only one trial of selpercatinib was performed (i.e. LIBRETTO-001), no meta-analysis was completed.

B.2.8 Indirect and mixed treatment comparisons

Summary of indirect treatment comparisons

Methodology

- A network meta-analysis (NMA) was performed to compare the efficacy of selpercatinib to other first line treatments relevant to the decision problem for the outcomes of ORR, PFS and OS.
- LIBRETTO-001 was a single-arm trial and therefore did not compare the efficacy of selpercatinib in advanced *RET* fusion-positive NSCLC directly to comparators relevant to the decision problem.
- In order to include the SAS1 trial population data from LIBRETTO-001 in the NMA it was therefore necessary to generate a pseudo-control arm.
- Individual patient data (IPD) from the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial were used to generate a pseudo-control arm. The LIBRETTO-001 selpercatinib arm and the pemetrexed plus platinum chemotherapy arm underwent propensity score matching (PSM) to account for any differences between trial populations.
- Both randomised effects and fixed effects models were assessed for all outcomes and the model which best fitted the data were used; in the base case a random effects model was selected for all outcomes.

Results

- Treatment with both selpercatinib (OR [95% CrI]: [redacted]) and pembrolizumab combination therapy (OR [95% CrI]: [redacted]) resulted in a [redacted] odds of ORR when compared to pemetrexed plus platinum based chemotherapy.
- In addition, treatment with both selpercatinib (HR [95% CrI]: [redacted]) and pembrolizumab combination therapy (HR [95% CrI]: [redacted]) had a lower hazard of progression or death (PFS) compared to pemetrexed plus platinum based chemotherapy.
- Similarly to PFS, treatment with both selpercatinib (HR [95% CrI]: [redacted]) and pembrolizumab combination therapy (HR [95% CrI]: [redacted]) demonstrated a [redacted] risk of death (OS) when compared to pemetrexed plus platinum based chemotherapy.

Uncertainties in the indirect treatment comparison

- The process of generating a pseudo-comparator arm to connect selpercatinib to the NMA was likely to be associated with inherent uncertainty. However, heterogeneity in patient baseline characteristics between LIBRETTO-001 and KEYNOTE-189 were adjusted for via a PSM to minimise any associated uncertainty.
- There were noticeable differences in the baseline characteristics of the studies included in the NMA including age, sex, proportion of Asian patients and the date of publication of the study. These differences may result in uncertainty in the estimates of treatment effect. However, a meta-regression was explored to assess the impact of these differences in the baseline characteristics on the NMA. None of the baseline characteristics were identified as significant.
- As most studies did not violate the proportional hazards assumption a synthesis assuming constant hazards was considered appropriate.
- To minimise potential biases the analysis used multiple methods recommended by NICE and the most robust statistical techniques for ITCs. Overall, the analyses presented provide evidence of the relative efficacy of selpercatinib in treatment-naïve patients with NSCLC given the limitations of existing data.

Conclusion

- Compared to comparators applicable to the decision problem, indirect treatment comparisons demonstrate that selpercatinib is associated with the greatest odds of a response and the lowest risk of progression or death.

LIBRETTO-001 was a single-arm trial and therefore did not compare the efficacy of selpercatinib in advanced *RET* fusion-positive NSCLC directly to comparators relevant to the decision problem. In order to generate relative efficacy estimates for selpercatinib versus comparators of interest it was therefore necessary to conduct an indirect treatment comparison.

The indirect treatment comparison comprised two steps:

1. Generation of a pseudo-control arm to selpercatinib through propensity score matching between the selpercatinib arm of LIBRETTO-001 and the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 RCT
2. Adjoining of selpercatinib to an NMA of first-line NSCLC treatments via the pseudo-control arms

B.2.8.1 Generation of the pseudo-comparator arm

The pseudo-control arm was simulated for the LIBRETTO-001 trial using IPD available for the pemetrexed plus platinum chemotherapy plus placebo arm from the KEYNOTE-189 RCT. KEYNOTE-189 included patients with non-squamous, metastatic NSCLC without sensitising EGFR or ALK mutations who had received no prior treatment for metastatic disease.[86] Control IPD were not available from any other trial identified in the SLR.

Propensity score matching was conducted between IPD from the SAS1 population of LIBRETTO-001 and the pemetrexed plus platinum chemotherapy plus placebo arm from the KEYNOTE-189 in order to account for differences in the two trial populations.

Propensity score matching approach

Current statistical methods that match one trial to another through use of IPD rely on the presence of some overlap in baseline population characteristics, particularly those that may have a prognostic impact on trial endpoints (e.g. smoking). Propensity score matching uses IPD from one data set to match to another data set. The propensity score for an individual is defined as the probability that the individual receives the treatment, given all the confounding covariates which are being controlled for in the analysis.[87] Specifically, matching aims to replicate randomisation by identifying control individuals who are similar to the treated individuals in one or more characteristics.[88] By matching the outcomes of individuals who differ in the treatment variable, but are otherwise observationally similar, this approach enables estimation of a treatment effect between the interventions under investigation.[88]

Differences in prognostic factors between the selpercatinib arm from LIBRETTO-001 and the placebo plus pemetrexed plus platinum chemotherapy arm from KEYNOTE-189 were adjusted for using propensity score estimated using a multivariable logistic regression approach.[87] The IPD from both trials was used to adjust for between-trial differences in observed baseline characteristics known to have an impact on prognosis (e.g., smoking status, sex) and to assess outcomes in a matched population. Guidance provided in NICE TSD17 informed the propensity score matching process.[88]

The covariates that were used as adjustment factors during propensity score matching are summarised in Table 21. In order to have data that allowed for matching, five patients from the LIBRETTO-001 dataset were excluded from the analysis; four patients has ECOG PS 2 at baseline and one patient with missing stage data. Ultimately [redacted] patients from the LIBRETTO-001 dataset were included in the PSM analysis. Adjustments relating to the presence of *RET* fusion were not made, due to the inconclusive prognostic nature of a *RET* fusion, as described in Section B.1.2.1.

A summary of the baseline patient characteristics of the LIBRETTO-001 and KEYNOTE-189 trial populations, alongside data showing the impact of adjustment for prognostic factors is provided in Table 21 below. The matching process better aligned key population characteristics between the selpercatinib and pseudo-control arm.

Table 21: Summary of patient characteristics of the KEYNOTE-189 and LIBRETTO-001 trial populations

Characteristic	Baseline characteristics		
		Before PSM	After PSM[a]
	LIBRETTO-001 (selpercatinib) (N = [redacted])	KEYNOTE-189 (pemetrexed and platinum chemotherapy + placebo) (N =206)	KEYNOTE-189 (pemetrexed and platinum chemotherapy + placebo) (N = 64)
Age (mean, years)	[redacted]	62.84	61.19
ECOG PS = 1, %	[redacted]	60.8%	68.8%
Female, %	[redacted]	47.1%	59.4%
Never smoked, %	[redacted]	12.3%	39.1%
Race: Asian, %	[redacted]	3.9%	12.5%
Race: Other[b], %	[redacted]	1.5%	4.7%
Stage III, %	[redacted]	0.5%	1.6%
Stage IV, %	[redacted]	99.5%	98.4%

[a]The analysis followed greedy matching algorithm. [b]Race:other includes non-white, non-Asian and unknown.
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Score; NSCLC: non-small cell lung cancer; PSM: propensity score matching.

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process described above to obtain significance tests for the estimated treatment effect, estimate hazard ratios and 95% credible intervals (CrIs) for selpercatinib versus the pseudo-control arm (Table 22). The hazard ratio was then introduced into the NMA for each outcome.

Table 22: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm)

Endpoint	Hazard ratio (95% CrI)	P value
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Abbreviations: CrI: credible interval; OS: overall survival; PFS: progression-free survival.

The Kaplan-Meier outputs for PFS and OS, from adjustment for prognostic factors through matching using propensity scores, are presented in Figure 11 and Figure 12, respectively.

Figure 11: Kaplan-Meier charts for PFS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following propensity score matching

Abbreviations: NSCLC: non-small cell lung cancer; PFS: progression free survival.

Figure 12: Kaplan-Meier charts for OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following propensity score matching

Abbreviations: NSCLC: non-small cell lung cancer; OS: overall survival.

B.2.8.2 NMA methodology

The primary aim of these NMAs was to provide relative treatment effect estimates of comparative efficacy between selpercatinib and comparators in treatment-naïve patients with advanced non-squamous NSCLC. The outcomes analysed were OS, PFS, and overall response rate (ORR).

An SLR was conducted in January 2016 and updated in June 2018, July 2020, July 2021 and April 2022 with the aim of identifying relevant clinical evidence for the efficacy and safety of selpercatinib or relevant comparators in treatment-naïve patients with locally advanced or metastatic non-squamous NSCLC receiving first-line and first-line to progression treatment (see Section B.2.1 and Appendix B.3). As the April 2022 SLR update did not identify any further studies that would be informative to the NMA relevant to this decision problem, studies up to the July 2021 update were assessed for inclusion in the NMA.

The number of potential comparators included in the analysis was larger than the number of comparators relevant to the decision problem of this submission, due to the requirement for this NMA to support the HTA processes of multiple countries. A full list of the eligibility criteria for inclusion in the NMA is provided in Appendix B.3.

Of the 70 studies reported in 77 peer-reviewed publications and 44 conference abstracts included in the clinical SLR up until the July 2021 update, 58 studies reported on first-line to progression treatments that fully met the SLR eligibility criteria. Of these 58 studies, 31 were connected and could be analysed in the NMA. The reasons for exclusion of the 27 studies is provided in Appendix B.3.

As described in B.2.8.1, generation of the pseudo-comparator arm enabled selpercatinib to be adjoined to the NMA and therefore relative treatment effects estimated between selpercatinib and relevant comparators. The full methodology of this NMA is provided in Appendix D.3.3 and Appendix D.3.4.

B.2.8.3 Indirect treatment comparison results

For ORR, the proportion of patients who experienced an objective response was modelled and treatment effect estimates were presented as OR with associated 95% CrIs. For OS and PFS, HRs representing treatment effect estimates with corresponding standard error values were synthesized in the model. In order to assess model fit, both random effect (RE) and fixed effect (FE) models were assessed for all outcomes, and the model which best fitted the data were used. For all outcomes a random effects model was selected for the base case analysis.

Overall response rate

The network diagram for ORR is presented in Figure 13.

Figure 13: Network diagram for treatments included in the NMA for ORR

Abbreviations: ATEZ: atezolizumab; BEV: bevacizumab; c:continuous; CAMR: Camrelizumab; CEMIPL: Cemiplimab; CrI: credible intervals; DURV: durvalumab; GEM: gemcitabine; HR: hazard ratios; i: induction; IPI: Ipilimumab; Nab-PAC: nab-paclitaxel; NIVO: nivolumab; PAC: paclitaxel; PEM: pemetrexed; PEMBRO: pembrolizumab; PLAT: platinum; RAM: ramucirumab; RE: random-effects; SEL: selpercatinib; SINT: sintilimab; TISL: tislelizumab.

The relative treatment effect estimate (OR) for ORR for comparators of interest versus pemetrexed plus platinum chemotherapy are presented in Table 23. An OR>1 is indicative of better response for the treatment in the row versus the reference treatment in the column. Treatment with both selpercatinib (OR [95% CrI]: [redacted]) and pembrolizumab combination therapy (OR [95% CrI]: [redacted]) resulted in a [redacted] odds of ORR when compared to pemetrexed plus platinum based chemotherapy. In addition, both pemetrexed plus platinum based chemotherapy and pembrolizumab combination therapy had a [redacted] odds of overall response when compared to selpercatinib (Table 24).

Forest plots depicting the effect of selpercatinib and pembrolizumab combination therapy versus pemetrexed plus platinum based chemotherapy, as well as both comparators compared to selpercatinib are presented in Figure 14.

Table 23: Relative treatment effect estimates expressed as pairwise ORs versus pemetrexed plus platinum chemotherapy (with 95% CrI) for ORR, random effects model

Treatment	Pairwise OR (95% CrI) versus pemetrexed + platinum chemotherapy
Selpercatinib	[redacted]
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]

Abbreviations: CrI: credible interval; OR: odds ratio; ORR: objective response rate.

Table 24: Relative treatment effect estimates expressed as pairwise ORs versus selpercatinib (with 95% CrI) for ORR, random effects model

Treatment	Pairwise OR (95% CrI) versus selpercatinib
Pemetrexed plus platinum based chemotherapy	[redacted]
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]

Abbreviations: CrI: credible interval; OR: odds ratio; ORR: objective response rate.

Figure 14: Posterior median ORs of active treatments versus (I) pemetrexed + platinum chemotherapy and (II) selpercatinib for ORR

Footnotes: *X-axes values do not cover 1, since the upper bound for all 95% CrIs was <1.
Abbreviations: ATEZ: atezolizumab; BEV: bevacizumab; c:continuous; CAMR: Camrelizumab; CEMIPL: Cemiplimab; CrI: credible intervals; DURV: durvalumab; GEM: gemcitabine; HR: hazard ratios; i: induction; IPI: Ipilimumab; Nab-PAC: nab-paclitaxel; NIVO: nivolumab; PAC: paclitaxel; PEM: pemetrexed; PEMBRO: pembrolizumab; PLAT: platinum; RAM: ramucirumab; RE: random-effects; SEL: selpercatinib; SINT: sintilimab; TISL: tislelizumab.

Progression-free survival

The network diagram for PFS is shown in Figure 15.

Figure 15: Network diagram for treatments included in the NMA for PFS

Abbreviations: ATEZ: atezolizumab; BEV: bevacizumab; c:continuous; CAMR: Camrelizumab; CEMIPL: Cemiplimab; CrI: credible intervals; DURV: durvalumab; GEM: gemcitabine; HR: hazard ratios; i: induction; IPI: Ipilimumab; Nab-PAC: nab-paclitaxel; NIVO: nivolumab; PAC: paclitaxel; PEM: pemetrexed; PEMBRO: pembrolizumab; PLAT: platinum; RAM: ramucirumab; RE: random-effects; SEL: selpercatinib; SINT: sintilimab; TISL: tislelizumab.

The relative treatment effect estimates for interventions of interest for PFS versus pemetrexed plus platinum chemotherapy are presented in Table 25. A HR<1 is indicative of a lower hazard of progression or death compared to the reference treatment. Treatment with both selpercatinib (HR [95% CrI]: [redacted]) and pembrolizumab combination therapy (HR [95% CrI]: [redacted]) had a lower hazard of progression or death compared to pemetrexed plus platinum based chemotherapy. In addition, both pemetrexed plus platinum based chemotherapy and pembrolizumab combination therapy were associated with a [redacted] hazard of progression or death when compared to selpercatinib (Table 26).

Forest plots depicting the effect of selpercatinib and pembrolizumab combination therapy versus pemetrexed plus platinum based chemotherapy, as well both comparators compared to selpercatinib are presented in Figure 16:.

Table 25: Relative treatment effect estimates expressed as HRs versus pemetrexed plus platinum chemotherapy (with 95% CrI) for PFS, random effects model

Treatment	Median HR (95% CrI) versus pemetrexed + platinum chemotherapy
Selpercatinib	[redacted]
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]

Abbreviations: CrI: credible interval; PFS: progression free survival.

Table 26: Relative treatment effect estimates expressed as HRs versus selpercatinib (with 95% CrI) for PFS, random effects model

Treatment	Median HR (95% CrI) versus selpercatinib
Pemetrexed plus platinum based chemotherapy	[redacted]
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]

Abbreviations: CrI: credible interval; OR: odds ratio; ORR: objective response rate.

Figure 16: Posterior median HRs of (i) comparators versus pemetrexed + platinum chemotherapy and (ii) comparators versus selpercatinib for PFS

Footnotes: *X-axes values do not cover 1, since all 95% CRIs upper bound was <1.
Abbreviations: ATEZ: atezolizumab; BEV: bevacizumab; c:continuous; CAMR: Camrelizumab; CEMIPL: Cemiplimab; CrI: credible intervals; DURV: durvalumab; GEM: gemcitabine; HR: hazard ratios; i: induction; IPI: Ipilimumab; Nab-PAC: nab-paclitaxel; NIVO: nivolumab; PAC: paclitaxel; PEM: pemetrexed; PEMBRO: pembrolizumab; PLAT: platinum; RAM: ramucirumab; RE: random-effects; SEL: selpercatinib; SINT: sintilimab; TISL: tislelizumab.

Overall survival

The network diagrams for OS is shown in Figure 17.

Figure 17: Network diagram for treatments included in the NMA for OS

Abbreviations: ATEZ: atezolizumab; BEV: bevacizumab; c:continuous; CAMR: Camrelizumab; CEMIPL: Cemiplimab; CrI: credible intervals; DURV: durvalumab; GEM: gemcitabine; HR: hazard ratios; i: induction; IPI: Ipilimumab; Nab-PAC: nab-paclitaxel; NIVO: nivolumab; PAC: paclitaxel; PEM: pemetrexed; PEMBRO: pembrolizumab; PLAT: platinum; RAM: ramucirumab; RE: random-effects; SEL: selpercatinib; SINT: sintilimab; TISL: tislelizumab.

The relative treatment effect estimates for interventions of interest for OS versus pemetrexed plus platinum chemotherapy are presented in Table 27.

Forest plots depicting the effect of selpercatinib and pembrolizumab combination therapy versus pemetrexed plus platinum based chemotherapy, as well both comparators compared to selpercatinib are presented in Figure 18.

A HR<1 is indicative of a lower hazard of progression or death compared to the reference treatment. Treatment with both selpercatinib (HR [95% CrI]: [redacted]) and pembrolizumab combination therapy (HR [95% CrI]: [redacted]) had a [redacted] hazard of death when compared to pemetrexed plus platinum based chemotherapy. In addition, as with PFS, both pemetrexed plus platinum based chemotherapy and pembrolizumab combination therapy were associated with a [redacted] hazard of death when compared to selpercatinib (Table 28).

Forest plots depicting the effect of selpercatinib and pembrolizumab combination therapy versus pemetrexed plus platinum based chemotherapy, as well both comparators compared to selpercatinib are presented in Figure 18.

Table 27: Relative treatment effect estimates expressed as HRs versus pemetrexed plus platinum chemotherapy (with 95% CrI) for OS, random effects model

Treatment	Pairwise HR (95% CrI) versus pemetrexed + platinum chemotherapy
Selpercatinib	[redacted]
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]

Abbreviations: CrI: credible interval; NR: not reported; HR: hazard ratio.

Table 28: Relative treatment effect estimates expressed as HRs versus selpercatinib (with 95% CrI) for PFS, random effects model

Treatment	Median HR (95% CrI) versus selpercatinib
Pemetrexed plus platinum based chemotherapy	[redacted]
Pembrolizumab + pemetrexed + carboplatin/cisplatin	[redacted]

Abbreviations: CrI: credible interval; OR: odds ratio; ORR: objective response rate.

Figure 18: Posterior median HRs of (i) comparators versus pemetrexed + platinum chemotherapy and (ii) comparators versus selpercatinib for OS

Footnotes: *X-axes values do not cover 1, since all 95% CRIs upper bound was <1.
Abbreviations: ATEZ: atezolizumab; BEV: bevacizumab; c:continuous; CAMR: Camrelizumab; CEMIPL: Cemiplimab; CrI: credible intervals; DURV: durvalumab; GEM: gemcitabine; HR: hazard ratios; i: induction; IPI: Ipilimumab; Nab-PAC: nab-paclitaxel; NIVO: nivolumab; PAC: paclitaxel; PEM: pemetrexed; PEMBRO: pembrolizumab; PLAT: platinum; RAM: ramucirumab; RE: random-effects; SEL: selpercatinib; SINT: sintilimab; TISL: tislelizumab.

B.2.8.4 Meta-regression

Several key areas of heterogeneity were identified between trials included in the NMA including baseline characteristics, sex distribution and proportion of Asian patients. For example, some studies were conducted exclusively in older populations (65-Plus and LOGIK1201). In addition, some studies only reported data on populations of mixed histologies despite the NMA primarily reporting on non-squamous subgroup data in line with the population of interest in LIBRETTO-001. A summary of the baseline characteristics of trials included in the NMA is provided in Appendix B.3.1.

To assess the impact of this between trial heterogeneity on the trial results, a meta-regression was performed to adjust for baseline characteristics between included studies. The meta-regression was restricted to studies with non-missing data and may be subject to limitations owing to the inclusion of potentially inaccurate data from studies with mixed histology data only. Various covariates including median age, sex, proportion of Asian patients and year of initial publication were included one at a time to assess whether they improved model fit. The analyses were performed for each endpoint (OR, OS and PFS). No baseline characteristics were identified as significant, suggesting the impact of any heterogeneity on the model results would be minimal.

B.2.8.5 Assessment of inconsistency

A key assumption of NMA is that the direct and indirect evidence are estimating the same parameters – meaning the evidence is consistent. For example, the treatment effect d_{BC} estimated by BC trials were assumed to be the same as the treatment effect estimated by the AC and AB trials if they had included treatment arms B and C. Therefore, the treatment effect inferred from indirect evidence through the NMA was assumed to be the same as the direct trial evidence. Where this was not the case, this was referred to as inconsistency.

Inconsistency in the NMAs was assessed using the inconsistency versus consistency method, which compares the residual deviances between the two. Prior to commencing the approach, each pairwise treatment comparison predicted from the NMA was compared to the corresponding comparison in a trial. This helped to identify where inconsistencies may be present and which studies or treatment arms could be contributing to these.

The results of the inconsistency assessment are provided in Table 29 below. In all assessments the consistency of DIC and residual deviance was similar (within the range of +/- 5 points) to the inconsistency of DIC and residual deviance. It is therefore concluded that no evidence of inconsistency was detected in the vast majority of analyses.

Table 29: Result of inconsistency assessment on the NMAs

Analysis	Consistency model		Inconsistency model		Number of data points
	Dbar	DIC	Dbar	DIC	
OS	26.58	48.22	27.90	51.57	31
PFS	26.38	48.16	26.97	50.81	28
ORR	45.69	86.76	43.28	85.76	51

Abbreviations: Dbar: mean sum of residual deviances; DIC: deviance information criterion; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.

B.2.8.6 Uncertainties in the indirect and mixed treatment comparisons

As discussed in Section B.1.1, due to the single-arm nature of the LIBRETTO-001 trial, it was necessary to generate a pseudo-comparator arm in order to connect selpercatinib to the NMA, a process that is associated with inherent uncertainty. IPD from the pemetrexed and platinum-based chemotherapy arm of KEYNOTE-189 was utilised to inform the control arm and propensity score matching undertaken to account for differences in the trial populations. Adjustment for the presence of *RET* fusion were not made owing to the inconclusive prognostic nature of *RET* (as discussed in Section B.1.2.1) and the increased uncertainty these adjustments would bring to the analyses. The prognostic nature of *RET* has been explored in a large US-based study, which found that after adjustment of baseline covariates, there was no significant difference in PFS and OS between patients with *RET* fusions and patients without, providing evidence that *RET* fusion may not be inherently prognostic.[31]

Several key areas of heterogeneity were identified between trials included in the NMA including sex distribution and proportion of Asian patients. These differences may result in uncertainty in the estimates of treatment effect and therefore as described in Section B.2.7 above, a meta-regression was performed to adjust the baseline characteristics of included studies. No baseline characteristics were identified as significant suggesting the impact of any between trial heterogeneity on the model results would be minimal.

The NMAs utilised for OS and PFS are dependent on the proportional hazards assumption. An assessment of proportional hazards identified that in three studies (ERACLE 2015, KEYNOTE-189 and KEYNOTE-189 Japan) assessing relevant comparators to the submission informing the PFS network and two studies (CameL and KEYNOTE-189 Japan) assessing relevant comparators to the submission informing the OS network, there was evidence that the proportional hazards assumption may not have held. Nevertheless, for the majority of included studies, there was no clear violation of proportional hazards, and it was therefore deemed appropriate to synthesise HRs, assuming constant hazards.

In order to minimise potential biases the analysis used methods recommended by NICE TSD17 and the most robust statistical techniques for ITCs.[89] [17]An extensive SLR of published and unpublished trials was conducted, excluding studies with methodological issues. This was followed by a thorough feasibility assessment to evaluate whether the studies included in the NMA are comparable in terms of treatment, disease, and relevant covariates. Furthermore, no evidence of inconsistency was detected in the assessment of inconsistency (see Section B.2.8.5).

Overall, the analyses presented provide evidence of the relative treatment effect estimate of selpercatinib versus relevant comparators in treatment-naïve patients with NSCLC in the context of limited data availability.

B.2.8.7 NMA conclusions

Overall, the results of the NMAs suggested that selpercatinib is likely to provide significant improvements in OS, PFS and ORR compared to both pemetrexed plus platinum based chemotherapy and pembrolizumab combination therapy in RET-fusion positive patients with advanced NSCLC.

B.2.9 Adverse reactions

Summary of LIBRETTO-001 safety analysis

- The safety of selpercatinib was assessed in all patients enrolled in LIBRETTO-001 (OSAS) (regardless of tumour type or treatment history) and patients with documented *RET* fusion-positive NSCLC (SAS) trial population
- Dose reductions were required in [redacted] ([redacted]) of the OSAS and [redacted] ([redacted]) of the *RET* fusion-positive NSCLC SAS, with the most common reason being AEs ([redacted] [40.8%]) and [redacted] in the OSAS and NSCLC SAS, respectively)
- In the OSAS, Grade 3 or 4 TEAEs were reported in 572 (71.9%) patients and 263 (73.9%) patients in the *RET* fusion-positive NSCLC SAS, irrespective of relatedness to selpercatinib.[77]
- Common TEAEs were easily monitored and reversible through dose interruption or addressed through dose reduction or concomitant medication
- In LIBRETTO-001, selpercatinib was well tolerated across all tumour types studied. The safety profile was characterised by recognisable and addressable toxicities. As a result, permanent discontinuation of selpercatinib due to TEAEs was infrequent in both the OSAS and SAS, meaning patients could consistently benefit from the highly efficacious anti-tumour activity of selpercatinib
- Overall, selpercatinib was shown to be well tolerated across patient populations and, considering the clinical efficacy demonstrated in *RET* fusion-positive NSCLC patients, selpercatinib has demonstrated a positive risk: benefit ratio in this population

The two safety analysis sets utilised in LIBRETTO-001 that were pertinent to this submission are as follows:

- The Overall Safety Analysis Set (OSAS, N = 796) includes all patients, regardless of tumour type or treatment history, who were enrolled in LIBRETTO-001 and received one or more doses of selpercatinib as of the 15th June 2021 data cut-off date
- The NSCLC Safety Analysis Set (SAS) (N = 356) includes all patients with documented RET fusion-positive NSCLC who were enrolled in LIBRETTO-001 and received one or more doses of selpercatinib as of the 15th June 2021 data cut-off date
- Both safety analysis sets included all 69 treatment-naïve patients with documented RET fusion-positive NSCLC who are the focus of this submission

From the time the informed consent form was signed until the end of the safety follow-up period (28 ± 7 days post last dose), all AEs were recorded on the appropriate electronic case report form (eCRF).[80] Events occurring prior to informed consent were considered medical history. Laboratory test abnormalities considered by the Investigator to be clinically relevant were to be reported in the eCRF as an AE. Each AE was evaluated for duration, severity and causal relationship with the investigational product or other factors. If toxicities due to PKs existed and were new or worsened from baseline, these were reported as AEs. If a new primary malignancy appeared, it was also to be considered an AE.[80]

B.2.9.1 Treatment duration and dosage

Informed by the Phase I dose escalation stage of LIBRETTO-001, the RP2D was 160 mg BID. The range of starting doses and average time on treatment were available for the SAS1 trial population (Table 30). Nearly all (66/69 [95.7%]) patients in the SAS1 trial population received the proposed starting dose of 160 mg BID.[62] The mean time on treatment was 18.27 months with

a range between 0.4 and 41.2 months. The relative median dose intensity was similar in the Overall Safety Population (94.46%) and in the RET fusion-positive NSCLC Safety Population (92.71%) (Table 31).

Dose reductions were required in [redacted] ([redacted]) patients in the OSAS and [redacted] ([redacted]) patients in the RET fusion-positive NSCLC SAS, with the most common reason being AEs ([redacted] [40.8%] and [redacted], respectively) (Table 32).[62] Dose interruptions occurred in [redacted] of the OSAS and [redacted] of the NSCLC SAS, with the most common reason being AEs ([redacted] and [redacted], respectively). There were [redacted] and [redacted] dose increases in the OSAS and NSCLC SAS, respectively.[62]

Table 30: Selpercatinib dosing (SAS1)

	SAS1 (treatment- naïve) (N = 69)
Starting dose, n (%)	
80 mg BID	[redacted]
160 mg BID (RP2D)	[redacted]
240 mg BID	[redacted]
Time on treatment, months	
Mean (SD)	[redacted]
Median (range)	[redacted]

Abbreviations: BID: twice daily; NSCLC: non-small cell lung cancer; QD: once daily; *RET*: rearranged during transfection; RP2D: recommended Phase II dose; SD: standard deviation.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80]

Table 31: Selpercatinib relative dose intensity (Safety Analysis Sets)

	SAS (*RET* fusion-positive NSCLC) (N = 356)	**OSAS (overall population) (N = 796)**
Relative dose intensity, n (%)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Category, n (%)		
≥90%	[redacted]	[redacted]
75–90%	[redacted]	[redacted]
50–75%	[redacted]	[redacted]
<50%	[redacted]	[redacted]

Abbreviations: NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection; SD: standard deviation.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80]

Table 32: Selpercatinib dose modifications (Safety Analysis Sets)

	SAS (*RET* fusion-positive NSCLC) (N = 356)	OSAS (overall population) (N = 796)
Dose reduction, n (%)		
Any	[redacted]	[redacted]
For AE	[redacted]	325 (40.8)
For other reason	[redacted]	[redacted]
Dose interruption, n (%)		
Any	[redacted]	[redacted]
For AE	245 (68.8)	510 (64.1)
For other reason	[redacted]	[redacted]
Dose increase, n (%)		
Any	[redacted]	[redacted]
Intra-patient escalation[a]	[redacted]	[redacted]
Re-escalation[b]	[redacted]	[redacted]
Other reason	[redacted]	[redacted]

Note: [a]Patients started at a lower dose during dose escalation that was subsequently increased; [b]Re-escalation after a dose reduction.
Abbreviations: AE: adverse event; NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Drilon *et al.* 2022.[77]

AEs were graded by the Investigator, when applicable, using the National Cancer Institute Common Terminology Criteria for Adverse Events.[90]

B.2.9.2 Treatment-emergent adverse events

AEs were defined to be treatment emergent if they started on or after the date of the first dose of selpercatinib (Study Day 1). For cases where it was not possible to ascertain treatment emergence, the event was classified as treatment emergent.

In the OSAS, 95% of AEs were considered to be related to selpercatinib but the majority were deemed to be of low severity, with 38.6% classed as Grade 3 or Grade 4 (Table 33). A similar pattern was observable in the NSCLC SAS. Permanent discontinuation of selpercatinib due to AEs were infrequent (3.1%) in the OSAS, with no predominant pattern among the individual AEs reported. One fatal TEAE within 28 days of last dose was attributed to selpercatinib in the OSAS, and zero deaths related to selpercatinib occurred in the NSCLC SAS.[77]

A high proportion of patients in the OSAS (99.9%) experienced at least 1 TEAE during treatment. The most common TEAEs, defined as occurring in 15% of patients or more, in the OSAS were: oedema (48.5%), diarrhoea (47.0%), fatigue (45.9%), dry mouth (43.2%), hypertension (41%), aspartate aminotransferase (AST) increase (36.7%), alanine transaminase (ALT) increase (35.7%), constipation (32.8%), abdominal pain (33.7%), rash (32.8%) and nausea (31.2%).[77] The vast majority of adverse events were classified as Grades 1–2 and deemed to be clinically

manageable in clinical practice. Rates of different TAEs were broadly similar between the OSAS and NSCLC SAS analysis sets, as presented in Table 34.[77]

Selpercatinib was therefore well tolerated across all tumour types studied in LIBRETTO-001, with a safety profile characterised by recognisable toxicities that were easily monitored, reversed with dose interruption or addressed through dose reduction or concomitant medication.

Table 33: Summary of safety trends (Safety Analysis Sets)

	SAS (*RET* fusion-positive NSCLC) (N = 356)	OSAS (overall population) (N = 796)
Any TEAE, n (%)		
All	356 (100.0)	795 (99.9)
Related to selpercatinib	341 (95.8)	756 (95.0)
Grade 3 or 4 TEAE, n (%)		
All	263 (73.9)	572 (71.9)
Related to selpercatinib	143 (40.2)	307 (38.6)
TEAE leading to treatment discontinuation, n (%)		
All	34 (9.6)	64 (8.0)
Related to selpercatinib	[redacted]	25 (3.1)
TE-SAE, n (%)		
All	[redacted]	[redacted]
Related to selpercatinib	[redacted]	[redacted]
Fatal TEAE		
All	[redacted]	[redacted]
Related to selpercatinib	0	1 (0.1)

Abbreviations: AE: adverse event; NSCLC: non-small cell lung cancer; *RET* rearranged during transfection; SAE: serious adverse event; TEAE: treatment emergent adverse event.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Drilon *et al.* 2022.[77]

Table 34: Common TEAEs of all grades (15% or greater in any Safety Analysis Sets)

Preferred term	Maximum severity incidence, n (%)			
	SAS (*RET* fusion-positive NSCLC) (N = 356)		OSAS (overall population) (N = 796)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Oedema	178 (50.0)	2 (0.6)	386 (48.5)	6 (0.8)
Diarrhea	184 (51.7)	15 (4.2)	374 (47.0)	40 (5.0)
Fatigue	153 (43.0)	8 (2.2)	365 (45.9)	25 (3.1)
Dry Mouth	163 (45.8)	0 (0.0)	344 (43.2)	0 (0.0)
Hypertension (AESI)	141 (39.6)	68 (19.1)	326 (41.0)	157 (19.7)
Aspartate aminotransferase increased	149 (41.9)	37 (10.4)	292 (36.7)	70 (8.8)

Alanine aminotransferase increased	147 (41.3)	53 (14.9)	284 (35.7)	91 (11.4)
Abdominal pain	101 (28.4)	5 (1.4)	268 (33.7)	20 (2.5)
Constipation	96 (27.0)	5 (1.4)	261 (32.8)	6 (0.8)
Rash	130 (36.5)	4 (1.1)	261 (32.8)	5 (0.6)
Nausea	112 (31.5)	4 (1.1)	248 (31.2)	9 (1.1)
Blood creatinine increased	92 (25.8)	10 (2.8)	227 (28.5)	15 (1.9)
Headache	94 (26.4)	3 (0.8)	220 (27.6)	11 (1.4)
Cough	87 (24.4)	0 (0.0)	184 (23.1)	0 (0.0)
Dyspnea	84 (23.6)	16 (4.5)	179 (22.5)	25 (3.1)
Vomiting	78 (21.9)	4 (1.1)	178 (22.4)	14 (1.8)
ECG QT prolongation (AESI)	74 (20.8)	21 (5.9)	168 (21.1)	38 (4.8)
Arthralgia	[redacted]	[redacted]	165 (20.7)	2 (0.3)
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Decrease appetite	73 (20.5)	1 (0.3)	[redacted]	[redacted]
Pyrexia	79 (22.2)	1 (0.3)	[redacted]	[redacted]
Urinary tract infection	70 (19.7)	8 (2.2)	[redacted]	[redacted]
Thrombocytopenia	74 (20.8)	20 (5.6)	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AE: adverse event; ECG: electrocardiogram; NSCLC: non-small cell lung cancer; *RET* rearranged during transfection; TEAE: treatment-emergent adverse event.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Drilon *et al.* 2022.[77]

B.2.9.3 Grade 3–4 treatment-emergent adverse events

In the OSAS, Grade 3 or 4 TEAEs were reported in 572 (71.9%) patients, irrespective of relatedness to study drug (Table 35). The most common Grade 3–4 events were hypertension (19.7%), ALT increase (11.4%), and AST increase (8.8%) in the OSAS. Despite the relatively high level of Grade 3–4 TEAEs observed in the OSAS, only a small proportion (307 [38.6%]) were considered by the Investigator to be related to selpercatinib. In the NSCLC SAS, 263 (73.9%) patients experienced Grade 3–4 TEAEs, irrespective of relatedness to selpercatinib (Table 35). A smaller proportion (143 [40.2%]) were considered by the Investigator to be related to selpercatinib. Common TEAEs mirrored the OSAS analysis set.[77]

Table 35: Grade 3–4 TEAE (occurring in ≥ 2% of patients)

Preferred term	SAS (*RET* fusion-positive NSCLC) (N = 356)		OSAS (overall population) (N = 796)	
	Any	Related to selpercatinib	Any	Related to selpercatinib
1 or more Grade 3–4 AEs	263 (73.9)	143 (40.2)	572 (71.9)	307 (38.6)
Hypertension	68 (19.1)	49 (13.8)	157 (19.7)	105 (13.2)

Preferred term	SAS (*RET* fusion-positive NSCLC) (N = 356)		OSAS (overall population) (N = 796)	
	Any	Related to selpercatinib	Any	Related to selpercatinib
Alanine aminotransferase (ALT) increased	53 (14.9)	41 (11.5)	91 (11.4)	72 (9.0)
Aspartate aminotransferase (AST) increased	37 (10.4)	24 (6.7)	70 (8.8)	50 (6.3)
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	15 (4.2)	8 (2.2)	40 (5.0)	16 (2.0)
Electrocardiogram QT prolonged	21 (5.9)	14 (3.9)	38 (4.8)	27 (3.4)
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	8 (2.2)	3 (0.8)	25 (3.1)	17 (2.1)
Dyspnoea	16 (4.5)	12 (3.6)	25 (3.1)	1 (0.1)
Thrombocytopenia	20 (5.6)	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]

Note: Grade 3–4 AEs related to selpercatinib are reported if occurring in 15% or more of the populations. Grade 3–4 AEs irrespective of their relationship are reported if occurring in 2% or more of the populations.
Abbreviations: AE: adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ECG: electrocardiogram; NSCLC: non-small cell lung cancer; NR: not reported; *RET* rearranged during transfection.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80] Drilon et al. 2022.[77]

B.2.9.4 Treatment emergent adverse events of special interest

Based on predictions from the *RET*-related literature, the preclinical toxicology programme and clinical experience with selpercatinib, AEs of special interest were identified for focussed analysis: ALT/AST increase, drug hypersensitivity reaction, hypertension and notable event QT prolongation. These special interest AEs are monitorable and reversible with successful dose modification strategies, which allow the majority of patients who experience these events to continue safely on therapy.[62]

ALT/AST increase

In the OSAS, the TEAE of AST increase was reported in 36.7% patients (28.8% related to selpercatinib; 8.8% Grade 3–4; 6.3% Grade 3–4 and related to selpercatinib). The TEAE of ALT increase was reported in 35.7% of OSAS patients (28.5% related to selpercatinib; 11.5% Grade 3–4; 9.0% Grade 3-4 and related to selpercatinib).[77] The majority of ALT and AST TEAEs were Grade 1 or 2.[80] Although ALT and AST TEAEs were the most common reasons for dose interruptions (ALT = [redacted]; AST= [redacted]) and reductions (ALT= [redacted]; AST= [redacted]), they led to permanent discontinuation in only [redacted] OSAS patients. In addition, no patients met Hy's Law criteria of drug induced liver injury.[80]

Hypersensitivity

Selpercatinib-related hypersensitivity was defined as patients who, early in their treatment course, experienced a constellation of symptoms or findings inclusive of maculopapular rash that was often preceded by fever and associated with arthralgias or myalgias. These were often followed by platelet decrease and/or transaminase increases or, less commonly, by a blood pressure decrease, tachycardia and/or creatinine increase.[80]

In the OSAS, drug hypersensitivity was observed in a [redacted] of patients who had one or more AE of hypersensitivity. The median time to first onset was [redacted] weeks (range: [redacted]). Grade 3 was the worst severity AE for [redacted] patients ([redacted]) and there were no Grade 4 or above hypersensitivity events. Hypersensitivity was deemed serious (all related to selpercatinib) in [redacted] OSAS patients.[80]

Overall, interventions through dose interruption and dose reduction were successful and, in most cases, patients were able to continue study drug treatment after dose reduction and/or interruption. Of the [redacted] OSAS patients with hypersensitivity reactions, [redacted] patients underwent dose reduction and [redacted] dose interruption. Only [redacted] of the [redacted] patients were reported to permanently discontinue selpercatinib due to a hypersensitivity reaction.[80]

Hypertension

In the OSAS, the AE of hypertension was reported in 41% of patients (28.1% considered related to selpercatinib), with 19.6% classified as Grade 3 and 0.1% classified as Grade 4. Of patients having experienced Grade 3–4 AEs of hypertension 13.2% were considered to be related to selpercatinib. A similar proportion of NSCLC SAS patients experienced hypertension (141[redacted][39.6%]), with 68 (19.1%) classified as Grade 3 and none as Grade 4.[77] Whilst hypertension was frequently reported, it can be managed easily and therefore did not result in substantial dose reductions or treatment interruptions. A minority of OSAS patients required dose interruption ([redacted]) and/or reduction (1.3%). [redacted] patient discontinued therapy due to an AE of hypertension.[62]

Moreover, of the 796 OSAS patients, [redacted] of patients had a reported chronic history of hypertension and [redacted] did not. The frequency of reported hypertension AEs was similar between these patients despite the difference in medical history.[77]

Notable Event-QT prolongation

Any grade ECG QT prolongation was reported for 168 patients (21.1%), with 130 (16.3%) considered related to selpercatinib in the OSAS.[77] The majority of events were Grade 1 or Grade 2. [redacted] patient had an AE of QTcF prolongation that was deemed serious. QTcF prolongation was manageable by selpercatinib dose interruptions ([redacted] patients) or reductions ([redacted] patients), while no action with drug was taken in [redacted] patients. No patients discontinued treatment due to QT prolongation in the OSAS.[62]

To date, [redacted] clinically significant TEAE related to QT prolongation such as treatment emergent arrhythmias, ventricular tachycardia, ventricular fibrillation, sudden death or Torsades de Pointes have been observed. QT prolongation events can be managed and reversed with successful dose modification strategies, allowing patients to continue safely on therapy.[62]

B.2.9.5 Safety conclusions

In LIBRETTO-001, selpercatinib was well tolerated across all tumour types studied. The safety profile was characterised by recognisable toxicities across both the NSCLC SAS and OSAS. These toxicities were easily reversable through dose interruption or addressed through dose reduction or concomitant medication. Whilst hypertension was frequently reported, it can be managed easily and therefore did not result in substantial dose reductions or treatment interruptions. As a result, permanent discontinuation of selpercatinib due to TEAEs were infrequent (8%), meaning patients could consistently benefit from the highly efficacious anti-tumour activity of selpercatinib. This favourable safety profile is as anticipated given the high specificity of selpercatinib for *RET*.[77]

B.2.10 Ongoing studies

Additional data to support the use of selpercatinib in patients with advanced *RET* fusion-positive NSCLC is expected, following completion of the ongoing LIBRETTO-001 trial. Additional data from this study may become available during the course of the evaluation, based on further data cuts in [redacted].

LIBRETTO-431 (NCT04194944) is a randomised, open-label, Phase 3 trial comparing selpercatinib to platinum-based and pemetrexed therapy, with or without pembrolizumab, as initial treatment of advanced or metastatic *RET* fusion-positive NSCLC.[14] Results for LIBRETTO-431 are expected in December 2023.[14] It is not anticipated for any data from this trial to become available during the course of this evaluation.

SIREN is an international multi-centre real world evidence (RWE) study observing the efficacy and safety of selpercatinib in clinical settings in 50 patients with *RET* fusion-positive NSCLC, 13 of which were treatment-naïve.[51] Current data are immature (median follow-up of 10 months) but further data collection is planned in the future.

Should selpercatinib receive a recommendation for use on the CDF, data would be collected from LIBRETTO-001, LIBRETTO-431 and SIREN during the course of CDF funding. Results from the LIBRETTO-431 trial will provide direct evidence for the effectiveness of selpercatinib compared to the primary comparators in this submission.

B.2.11 Interpretation of clinical effectiveness and safety evidence

Principal findings of the clinical evidence base

In line with the final scope, this submission positions selpercatinib as monotherapy in treatment-naïve patients with advanced non-squamous *RET* fusion-positive NSCLC. The key source of efficacy and safety evidence supporting selpercatinib in this position is the LIBRETTO-001 trial. LIBRETTO-001 is an ongoing, multicentre, single-arm, open-label Phase I/II study. Phase I was designed to understand the PK, safety and MTD of selpercatinib. Phase II was designed for the preliminary assessment of selpercatinib efficacy and safety in patients with *RET*-altered solid tumours, with ORR as the primary outcome measure and DOR, PFS and OS as secondary measures.[62]

A high ORR was observed in treatment-naïve advanced *RET* fusion-positive NSCLC patients receiving selpercatinib during the LIBRETTO-001 trial (84.1%).[78] These results provide tangible evidence for the anti-tumour activity of selpercatinib in advanced NSCLC. In addition, with 66.1%

of patients predicted to remain in response at 12 months, the anti-tumour activity of selpercatinib is durable, providing a clinically meaningful delay in disease progression that works to maintain patient quality of life. Moreover the majority (53.6%) of patients showed no disease progression, with a median PFS of 21.95 months.[77] Although OS data are immature, radiographical evidence of tumour shrinkage (response rate) in cancer patients has been considered sufficient to predict clinical benefit and an improvement in OS.[48, 91] Kaplan-Meier estimates suggest that 70.6% of treatment-naïve advanced NSCLC patients will remain progression free at 12 months, indicating level of disease control and stabilisation with selpercatinib, which is supported by a high predicted OS (92.7%). Crucially, these clinical outcomes are supported by patient reported outcomes, with 28.3% of evaluated patients reporting a sustained improvement in their global health status via EORTC-QLQ-C30 at 15th June 2021 cut-off (Section B.2.5.5).

The results of the ITC indicated that treatment with both selpercatinib (OR [95% CrI]: [redacted]) and pembrolizumab combination therapy (OR [95% CrI]: [redacted]) resulted in a [redacted] odds of ORR when compared to pemetrexed plus platinum based chemotherapy. In addition, treatment with both selpercatinib (HR [95% CrI]: [redacted]) and pembrolizumab combination therapy (HR [95% CrI]: [redacted]) had a lower hazard of progression or death (PFS) compared to pemetrexed plus platinum based chemotherapy. Similarly to PFS, treatment with both selpercatinib (HR [95% CrI]: [redacted]) and pembrolizumab combination therapy (HR [95% CrI]: [redacted]) demonstrated a [redacted] risk of death (OS) when compared to pemetrexed plus platinum based chemotherapy (Section B.2.8).

Selpercatinib has also demonstrated a tolerable safety profile across all trial patients (regardless of tumour type), with Grade 3–4 AEs related to selpercatinib seen in 38.6% of patients in the OSAS, a [redacted] dose reduction rate and a discontinuation rate due to AEs of 64.1%.[77] Similar results were reported in patients with *RET* fusion-positive NSCLC specifically, with Grade 3–4 related to selpercatinib AEs reported in 40.2% patients, dose reductions reported in [redacted] of patients and discontinuations due to AEs in 68.8% of patients in the SAS.[77] These results align with biological expectation, with the specificity of selpercatinib to *RET* hypothesised to provide efficacious anti-tumour activity alongside a lower toxicity profile compared with non-targeted systemic therapies. This allows most advanced NSCLC patients to experience the clinical benefit of selpercatinib treatment, without having to break or discontinue treatment.

Consequently, clinical effectiveness and safety evidence from LIBRETTO-001 demonstrates that selpercatinib is well-tolerated and provides a clinically meaningful impact on the lives of treatment-naïve patients with advanced (Stage IIIB and IV) *RET* fusion-positive NSCLC. The high rates of durable response of *RET* fusion-positive NSCLC tumours to selpercatinib treatment, paired with self-reported improvements in patients' quality of life, support the case for the use of selpercatinib in treatment-naïve patients with *RET* fusion-positive NSCLC who require systemic therapy in UK clinical practice.

Strengths and limitations of the clinical evidence base

LIBRETTO-001 is highly relevant to the decision problem in terms of patient population and the outcomes considered. The study includes treatment-naïve patients with confirmed advanced, non-squamous, *RET* fusion-positive NSCLC, which is the patient population under consideration in this submission. The molecular sequencing of tumour samples was also consistent with NHS practice, given the ongoing transition to Genomic Hubs for NGS testing, with over [redacted] of patients assessed using NGS.[66]

[redacted] based in the UK, enrolling [redacted] patients into the OSAS and [redacted] into the SAS1 population. However, the higher proportion of women (62.3%), the low median age at diagnosis for NSCLC (63 years) and the higher proportion of patients that have never smoked (69.6%) compared to the general lung cancer population, reported in the SAS1 trial population is consistent with the patient profile for *RET* fusion-positive NSCLC reported in the literature,[2, 37] and is anticipated to mirror the real-world patient profile in England.[77] The generalisability of the LIBRETTO-001 trial to the UK was confirmed by two UK expert clinicians.[17] Accordingly, the efficacy and safety results from LIBRETTO-001 are likely to be highly generalisable to patients that would be treated with selpercatinib in the NHS. In addition to their relevance to the decision problem, the outcomes measured in LIBRETTO-001 are clinically meaningful for patients, as it has been found that increased duration of response and delay in disease progression bring quality of life benefits to patients.[6] Both PFS and OS are additionally important for informing the cost-effectiveness analysis.

Although evidence for the efficacy and safety of selpercatinib in *RET* fusion-positive NSCLC is in part derived from Phase I of LIBRETTO-001, which consisted of a dose escalation study, the majority [redacted] of treatment-naïve patients initiated treatment on the 160 mg BID dose which is anticipated to be the licensed dose for use in UK clinical practice.

A key limitation of the evidence base was that no randomised clinical trial evidence was available for selpercatinib with which to compare efficacy and safety to relevant comparators, with the single-arm LIBRETTO-001 trial representing the primary source of evidence for selpercatinib in treatment-naïve RET fusion-positive NSCLC. This necessitated the use of advanced ITC techniques to make comparisons to interventions relevant to the decision problem. The process of generating pseudo-comparator arms to connect selpercatinib to the NMA introduced inherent uncertainty. Several key areas of heterogeneity were identified between trials included in the NMA including, baseline characteristics, sex distribution and proportion of Asian patients however none were identified as significant suggesting the impact of any between trial heterogeneity on the model results would be minimal (see Section B.2.8.4). Additionally, in three studies assessing relevant comparators to the submission informing the PFS network and two studies assessing relevant comparators to the submission informing the OS network,the proportional hazards assumption may not have held. However, as there were no clear violations of proportional hazards in the majority of studies included in the NMA it was deemed appropriate to assume constant hazards.

OS data from LIBRETTO-001 were also immature, with a non-estimable median OS, however the majority of patients (71%) remained alive at a median follow-up of 25.2 months. Although initial results from LIBRETTO-001 are promising, confirmatory data supporting the effect of selpercatinib on OS is desirable.[77]

To confirm the benefits of selpercatinib in treatment-naïve *RET* fusion-positive NSCLC patients observed in the LIBRETTO-001 trial, Eli Lilly and Company is conducting a Phase III study (enrolment initiated in Q1 2020) in treatment-naïve patients for metastatic *RET* fusion-positive NSCLC, which is planned to enrol 250 participants. The primary endpoint is PFS by IRC and the study compares to pemetrexed plus platinum chemotherapy, with or without pembrolizumab. It is therefore planned for preliminary clinical effectiveness and safety data for selpercatinib versus the primary comparators to the submission to become available, which is of importance should selpercatinib be recommended for use under the CDF.

Additionally, as the Phase I/II LIBRETTO-001 trial is currently ongoing, it is anticipated that there will be OS data with increased maturity. Furthermore, a real world evidence (RWE) study, SIREN, observing the efficacy in clinical settings of selpercatinib in 50 patients with *RET* fusion-positive NSCLC, is ongoing.[51]

Selpercatinib therefore demonstrated high levels of efficacy in LIBRETTO-001, combined with a tolerable safety profile. This is likely to lead to an improvement in HRQoL, as indicated by EORTC data collected as part of the study, and an extension of life. Moreover, an ITC analysis showed that these efficacy benefits are superior to current standard of care for *RET* fusion-positive NSCLC patients (Section B.2.8). Accordingly, selpercatinib is expected to fulfil a currently unmet need for an efficacious and tolerable treatment option for treatment naïve patients with advanced *RET* fusion-positive NSCLC.

B.3 Cost-effectiveness

Summary of the cost-effectiveness analysis

- A cost-effectiveness model was developed to assess the cost-effectiveness of selpercatinib in treatment naïve-adults with *RET* fusion-positive NSCLC.
- The patient population was informed by data from the supplementary analysis set 1 (SAS1) (N=69) from the LIBRETTO-001 trial.
- The model adopted a partitioned survival approach with three health states: progression free (PF), progressed disease (PD) and dead, over a lifetime time horizon (25 years).
- Parametric survival functions were applied in order to extrapolate PFS and OS data for selpercatinib and the pemetrexed plus platinum chemotherapy arm, which also functioned as the pseudo-control (reference) arm generated through the process (see Section B.2.8).
- In order to generate extrapolations for pembrolizumab combination therapy for PFS and OS, the hazard ratio (HR) generated through the network meta-analysis (NMA) was applied to the reference arm.
- TSD 14 guidance was followed to determine the most appropriate extrapolations for selpercatinib and comparators, including seeking expert clinical opinion for clinical plausibility.[92]
- Costs included in the model were drug acquisition, drug administration, monitoring, subsequent therapies, health state costs, adverse events (AEs) and end of life costs.
- Utility values for the PF and PD states were derived from values obtained from the LIBRETTO-001 trial via the EORTC QLQ-C30 questionnaire. These values were mapped to EQ-5D-3L in line with the methods described in Young *et al*. (2015).[93]

Base case cost-effectiveness results

- The treatment-naïve *RET* fusion positive NSCLC population was calculated to have a severity modifier of 1.2 on the QALY, equating to a willingness-to-pay (WTP) threshold of £36,000 per QALY.
- Including the existing PAS, selpercatinib was associated with deterministic pairwise incremental cost-effectiveness ratios (ICERs) of £35,883 and £5,264 per QALY versus pemetrexed plus platinum based chemotherapy and pembrolizumab combination therapy, respectively.
- In the probabilistic base case analysis, selpercatinib was associated with probabilistic pairwise ICERs of £36,025 and £5,209 per QALY gained, versus pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy, respectively.
- The results illustrate that versus both comparators, selpercatinib is cost-effective at a WTP threshold of £36,000 per QALY.

Sensitivity and scenario analyses

- The results of the deterministic sensitivity analyses showed that only a small number of inputs had a significant impact on the ICER when varied to their limits across all pairwise comparisons, illustrating the robustness of the model to variation in input parameters
- With regards to structural variation, the results of the scenario analyses demonstrated that the ICERs were most sensitive to variations in the survival functions used to extrapolate OS and the distribution of subsequent therapies. As noted above, significant importance was placed on the clinical plausibility of the extrapolations used in the base case, with feedback sought from expert oncologists practising in the NHS in order to ensure the selection of the most appropriate functions due to the data immaturity.

Conclusion

- The cost-effectiveness analysis illustrates that selpercatinib represents a cost-effective use of NHS resources versus established care for treatment-naive *RET* fusion-positive NSCLC patients.

B.3.1 Published cost-effectiveness studies

An economic systematic literature review (SLR) was conducted on the 4th March 2019 to identify all relevant literature published on previous economic models of first line treatments in patients with advanced and/or metastatic NSCLC, and to review appraisals and criticisms of these models by health technology assessment (HTA) agencies. Full details of the economic SLR search strategy, study selection process and results are reported in Appendix G. In total, 57 unique UK economic evaluations were identified by the SLR.

B.3.1.1 Economic analysis

A cost-effectiveness model was developed to assess the cost effectiveness of selpercatinib in treatment-naïve adults with advanced *RET* fusion-positive NSCLC.

B.3.1.1 Patient population

The economic analysis considered treatment-naïve adults with *RET* fusion-positive advanced NSCLC, informed by data from the SAS1 population (N=69) from the LIBRETTO-001 trial. The SAS1 population is reflective of the decision problem defined in Section B.1.1 and the licence extension for selpercatinib.

B.3.1.2 Model structure

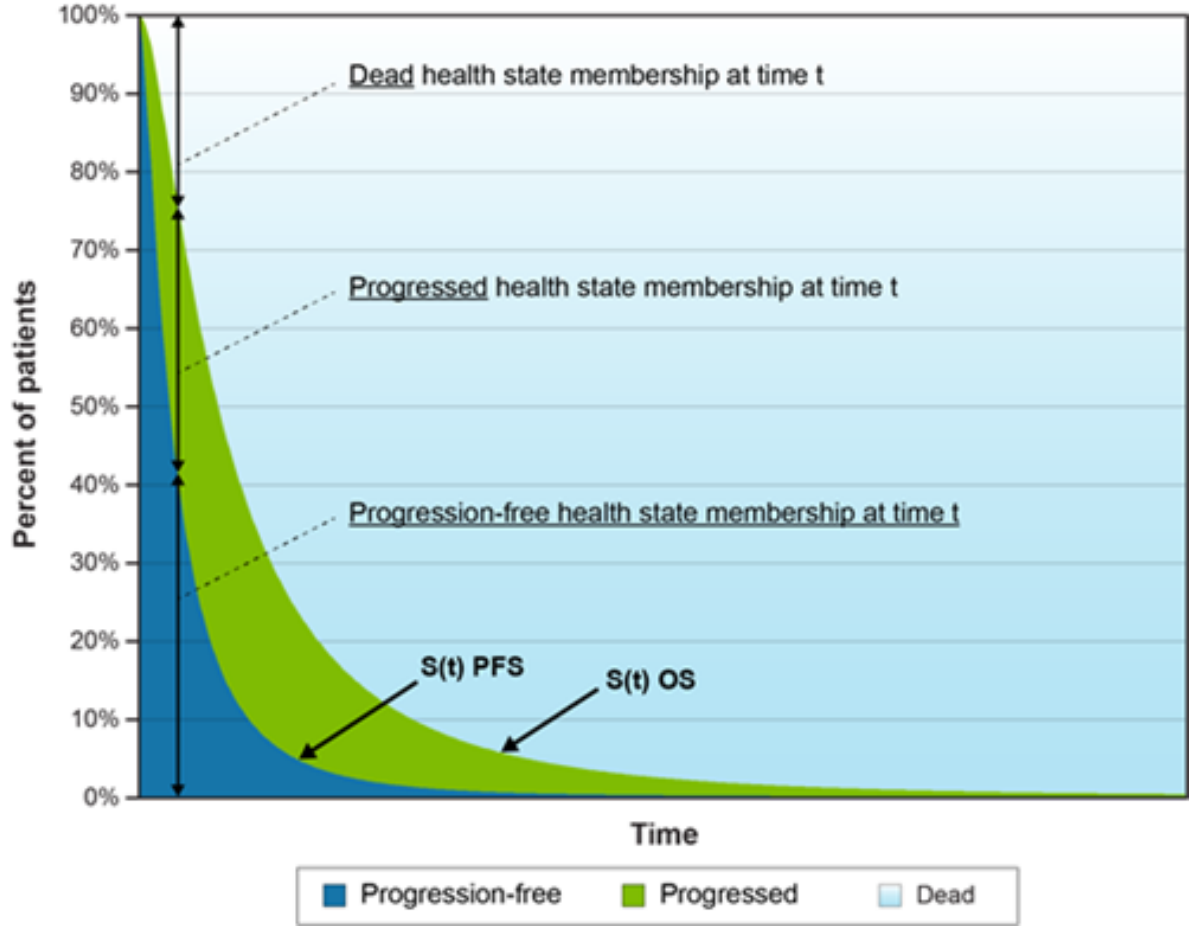
The cost-effectiveness model was constructed in Microsoft Excel and adopted a cohort-based partitioned survival model approach,[94] in line with a number of prior NICE appraisals in NSCLC, including TA760, TA705 and TA683.[12, 68, 70]

The model comprised three mutually exclusive health states, as follows:

- **Progression-free:** Patients' disease is in a stable or responding state and not actively progressing. Patients in this state are assumed to incur costs associated with treatment acquisition, administration, treatment monitoring, medical management of the condition and the management of Grade 3/4 AEs. Patients also experience a higher utility compared with progressed disease.
- **Progressed:** Patients have met the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria for disease progression. Patients in this state may continue their allocated therapy for a time and/or have subsequent anti-cancer therapy and incur costs associated with treatment acquisition, administration, medical management of the condition and terminal care. Patients experience a lower utility compared with progression-free disease
- **Dead:** Patients no longer incur costs, life years or utilities.

A graphical depiction of the partitioned survival model approach is presented in Figure 19 below.

Figure 19: Partitioned survival model structure



Notes: The data in the figure are fictitious and used for illustrative purposes only. S(t) PFS is the survival function describing the probability that a patient remains in the progression-free health state beyond a specific time point (t) from model entry. S(t) OS is the survival function describing the probability that a patient survives in the progression-free or the progressed health states beyond a specific time point (t) from model entry. Membership in the progressed health state is determined by subtracting the progression-free state membership from the dead state membership.
Abbreviations: OS: overall survival; PFS: progression-free survival.

Adults with treatment-naïve *RET* fusion-positive NSCLC were modelled to enter the partitioned survival model in the progression-free health state and to receive either selpercatinib or one of pembrolizumab combination therapy or pemetrexed plus platinum-based chemotherapy. The proportion of patients in each heath state at each model cycle was then determined for each therapy from cumulative survival probabilities from PFS and OS parametric survival functions, as follows:

- The proportion of patients occupying the progression-free state was calculated as the proportion alive and progression-free (based on PFS parametric survival functions)
- The proportion of patients occupying the progressed state was calculated as the proportion alive (based on OS parametric survival functions) minus the proportion of patients alive and progression-free (based on PFS parametric survival functions)
- The proportion of patients occupying the death state was calculated as the proportion who had died (based on OS parametric survival functions)

Patients were redistributed among the three health states at each weekly model cycle.

The model structure does not allow for patients to improve their health state, which reflects the progressive nature of the condition. The death health state is an absorbing health state.

The partitioned survival approach allows for modelling of OS and PFS based on study-observed events, which facilitates the replication of within-trial data in the model. This means that the model is expected to accurately reflect disease progression and the observed survival profile of patients treated with selpercatinib and comparator therapies. Importantly, the PFS and OS curves can be constructed from summary Kaplan-Meier data in the absence of patient-level data. Given the reliance on published summary data rather than patient-level data for comparator therapies, this was an important benefit of this model structure.

Features of the cost-effectiveness analysis

Costs and health state utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle, which were totalled at the end of the time horizon. Cost components considered included: drug acquisition, drug administration, treatment monitoring, medical management of the condition, subsequent treatments, AEs, and terminal care. Effectiveness measures included life years (LYs) and QALYs. The ICER of selpercatinib versus each comparator was assessed.

In line with the NICE reference case,[95] the analysis was conducted from the perspective of the National Health Service (NHS) and Personal Social Services (PSS). A lifetime time horizon of 25 years was chosen. This is similar to values chosen in recent NICE appraisals,[12, 68, 70] and was deemed reasonable based on the mean baseline age of patients in LIBRETTO-001 ([redacted] years) and the average life expectancy of advanced NSCLC patients. A 1-week cycle length was considered in the base case as this was deemed sufficiently granular to capture the dosing schedules of the treatments included in the model. Due to the short cycle length, it was not deemed necessary to include a half-cycle correction. Costs and effects were discounted at 3.5% annually.[95] The economic analysis is conducted using recent estimates of resource use and treatment costs available from published sources, including NHS reference costs for 2019–2020, electronic market information tool (eMIT), Personal Social Services Research Unit 2021 and the British National Formulary 2022.[96, 97]

The features of the analysis were based on previous NICE evaluations including:

- TA683: pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous NSCLC[68]
- TA760: selpercatinib for previously treated RET fusion-positive advanced NSCLC[12]
- TA654: osimertinib for untreated EGFR mutation-positive NSCLC[98]
- TA812: pralsetinib monotherapy for RET fusion-positive advanced non-small-cell lung cancer[18]

A summary of the key features of these four appraisals and justification for the design of the cost-effectiveness analysis for selpercatinib in treatment-naïve patients with advanced *RET* fusion positive NSCLC is provided in Table 36.

Table 36: Features of the economic analysis

Factor	Previous models in advanced NSCLC				Current appraisal	
	TA683[68]	TA654[98]	TA760[12]	TA812[18]	Chosen values	Justification
Model structure	Partitioned survival model	Partitioned survival model	Partitioned survival model	Partitioned survival model	Partitioned survival model	A partitioned survival model may accurately reflect disease progression and the observed survival profile of patients treated with selpercatinib and comparator therapies, and is in line with recent previous NICE appraisals in NSCLC.
Time horizon	Lifetime horizon (20 years)	Lifetime horizon (20 years)	Lifetime horizon (25 years)	Lifetime horizon (25 years)	Lifetime horizon (25 years)	A lifetime time horizon captures all costs and QALYs associated with selpercatinib and comparators, and is in line with the NICE reference case.[99]
Cycle length	1 week	Not reported	1 week	1 month	1 week	A 1-week cycle length was deemed appropriate given the rate at which relevant clinical events may occur, and the frequency at which treatment regimens are administered.
Half-cycle correction	Not reported	Not reported	No	Yes	No	Due to the short length of the cycle it was not deemed necessary to include a half-cycle correction.
Treatment waning effect?	Yes – gradual waning from Year 2 (treatment interruption) to Year 5	Not reported	No	No	No	PFS and OS parametric survival curve selections for selpercatinib and comparators were validated by UK clinical expert opinion on the most clinically plausible long-term efficacy estimates.
Source of utilities	Combined method of time to death and progression-based utilities derived from EQ-5D data collected	PF: 0.794 PD: 0.678	***Pre-treated*** PF: 0.78 PD: 0.628 (preferred values by the Committee)[100]	***Untreated*** TA654[98] preferred values by the Committee PF: 0.794 PD: 0.678	PF: 0.801 PD: 0.749	HSUVs for progression free and progressed disease were derived from EORTC-QLQ-C30 data obtained from the LIBRETTO-001 trial and mapped to EQ-5D-3L data using the methods described by Young et al. (2015).[93]

	in KEYNOTE-189			***Pre-treated*** TA713[101] preferred values by the Committee PF: 0.713 PD: 0.628		
Source of costs	• Not reported	• Sourced from BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care	• NHS Reference Costs • PSSRU • Drug acquisition • Administration • Subsequent treatments • Monitoring • Health states • End of life • Adverse events	• NHS Reference Costs • PSSRU • BNF • eMIT • Drug acquisition • Administration • Subsequent treatments • Health states • End of life • AEs	• NHS Reference Costs • PSSRU • BNF • eMIT • Drug acquisition • Administration • Subsequent treatments • Treatment monitoring • Medical management of the condition • End of life • AEs	Established sources of costs within the NHS. In line with the NICE reference case. A proportional cost associated with the detection of *RET* fusion-positive patients was included in the model for prior (pre-treated) evaluation for selpercatinib (TA760)[12], due to the implementation of national genomic testing provided by the NHS. However, we believe this may underestimate the cost-effectiveness of selpercatinib in this indication given the ongoing establishment of Genomic Hubs, as described in Section B.1.3.2, which would make *RET*-fusion testing, along with testing for other genetic drivers, part of routine NHS practice.[102] Accordingly, costs for *RET* fusion testing are considered to be absorbed by the healthcare system.

[a]Costs of adverse events were calculated multiplying the length of hospital stay resulting from adverse events, estimated by trial data, with hospitalisation costs.
Abbreviations: BNF: British National Formulary; CMU: Commercial Medicines Unit; eMIT: electronic market information tool; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; PD: progressed disease; PF: progression-free; PSSRU: Personal Social Services Research Unit; QALY: quality adjusted life year; RET: rearranged during transfection.

B.3.1.3 Intervention, technology and comparators

Intervention

The intervention of interest is selpercatinib (160 mg) administered twice daily. This is in line with the existing licensed dose for selpercatinib in advanced pre-treated *RET* fusion-positive NSCLC.[20] It is advised that treatment is administered until disease progression or unacceptable toxicity occurs.

Comparators

As discussed previously in Section B.1.2, selpercatinib, a selective inhibitor for *RET* receptor tyrosine kinase, is one of the first therapies in its class, and if recommended, would be the first RET inhibitor available for patients in the advanced, untreated setting in the UK.

As noted in Section B.1.3, there are a number of treatment options for treatment-naïve patients diagnosed with Stage IIIB–C and IV NSCLC in UK clinical practice who exhibit or do not exhibit genetic markers. Given there are currently no treatments available in the UK that target *RET* fusion-positive NSCLC, this patient population is currently offered treatment with the same set of therapies as patients not exhibiting genetic markers. This practice is supported by the finding that patients with oncogene-driven NSCLC, such as *RET* fusion-, *EGFR*-, *ALK*- or *ROS-1*-positive cancer, typically have just one genetic marker, and thus would not benefit from other oncogene-targeted therapies.[5, 10] Accordingly, in UK clinical practice, selpercatinib would replace treatments that are currently recommended for the treatment of advanced, non-squamous NSCLC tumours that do not exhibit any recognised genetic mutations. In line with clinical feedback received during the evaluation of pralsetinib (TA812) and feedback collected by Eli Lilly from expert oncologists practising in the UK, it is expected that selpercatinib would primarily replace pembrolizumab combination therapy (TA683)[68] and pemetrexed plus platinum chemotherapy (TA181)[72] in the treatment pathway for treatment-naïve patients.[17, 18]

Details of the interventions included in the cost-effectiveness model are presented in Table 37.

Table 37: Details of interventions included in the model

Intervention (patient subgroup)	Planned dosage per treatment cycle	Duration of treatment	Administration route	Source
Selpercatinib	160 mg twice daily	In 28-day cycles until progressive disease or unacceptable toxicity, or any other reasons for treatment discontinuation	Oral	Drilon *et al.* 2020a.[65]
Pembrolizumab + pemetrexed + platinum chemotherapy	Pembrolizumab: 200 mg Carboplatin: AUC 5 mg/mL x min Pemetrexed: 500 mg/m^2	In 21-day cycles up to 2 years or until disease progression Up to 4 x 21-day cycles or until disease progression Up to disease progression	IV	Planchard *et al.* 2018;[103] TA557;[104] Langer *et al.* 2016.[105]
Pemetrexed + platinum chemotherapy	Pemetrexed: 500 mg/m^2 Carboplatin: AUC 5 mg/mL x min	Up to disease progression Up to 6 x 21-day cycles or until disease progression	IV	Dobele *et al.* 2015.[106]

Abbreviations: AUC: area under the curve; IV: intravenous.

B.3.2 Clinical parameters and variables

B.3.2.1 Baseline characteristics

The baseline characteristics for the model population are provided in Table 38.These inputs were based on the baseline characteristics of patients who received selpercatinib in the LIBRETTO-001 trial. As noted in Section B.2.3.4, and confirmed by clinical expert feedback, the baseline characteristics of the LIBRETTO-001 trial were considered to be representative of patients in UK clinical practice.[17]

Table 38: Baseline characteristics for the model population

Model parameter	Value	Source
Mean age, years	[redacted]	LIBRETTO-001 (SAS1)
Percentage female, %	62.3	LIBRETTO-001 (SAS1)
Mean weight, kg	[redacted]	LIBRETTO-001 (SAS1)

Abbreviations: SAS1: Supplemental Analysis Set 1.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80]

B.3.2.2 Progression free survival

As described in Section B.3.2.2, the proportion of patients in each heath state at each monthly model cycle was determined for each therapy directly from cumulative survival probabilities for PFS.

- As described in Section B.2.8.2, a matched reference arm was generated to complement the PFS and OS data generated for selpercatinib from the single-arm trial LIBRETTO-001.
- In order to inform long-term estimates of PFS in the model for selpercatinib and comparators, it was necessary to extrapolate the PFS data generated for selpercatinib and the reference arm (pemetrexed plus platinum chemotherapy) through the application of parametric survival functions. PFS functions for pembrolizumab combination therapy were then constructed through the application of a HR to the reference arm extrapolation (Table 39), as generated through the NMA described in Section B.2.8.2.

Table 39: PFS HR applied to reference arm (pemetrexed + platinum chemotherapy)

Drug (Patient subgroup)	HR (95% CrI)
Pembrolizumab + pemetrexed + platinum chemotherapy	[redacted]

Abbreviations: CrI: Credible interval; HR: hazard ratio; PFS: progression-free survival.

Approach to parametric survival function selection

The methods for survival analysis to identify the most appropriate parametric survival functions to extrapolate the selpercatinib and the reference arm followed the recommendations of NICE Decision Support Unit (DSU) TSD 14.[92] Specifically, goodness-of-fit statistics were calculated to understand which parametric form had the best fit to the data, assessment of visual fit was conducted, and clinical expert opinion was sought regarding the plausibility of the long-term extrapolations of each function.[17]

Survival functions were fitted to the Kaplan-Meier data for selpercatinib and the reference arm generated via the PSM process described in Section B.2.8. Due to the generation of extrapolations for pembrolizumab combination therapy through application of a HR to the reference arm, it was deemed statistically appropriate to explore functions to which the proportional hazards assumption applies, specifically, the exponential, Gompertz and Weibull functions. Accordingly, the fit of these functions to the Kaplan-Meier data across treatment arms for selpercatinib, the reference arm and pembrolizumab combination therapy was attempted and assessed initially (it was assumed that the best-fitting function to the reference arm would also fit the comparator arms). If visual assessment and clinical plausibility was not met, then different models were explored for each arm, to ensure that clinically valid estimations were being made.

In addition, in the interest of maximising clinical plausibility of the extrapolations in the *RET* fusion-positive population, exploration of the fit of a further range of survival functions was also conducted, specifically, accelerated failure time (AFT) models (gamma, lognormal and loglogistic functions), stratified functions and spline models. Stratified models refer to models where all parameters can vary by treatment. These models relax the assumptions of proportional hazards or constant acceleration factors and allow for parametric models to be fitted to both arms (i.e. selpercatinib and the reference arm) at the same time, rather than fitted individually to each arm. Although spline-based models may not have a theoretical distribution, they can be used to fit survival curves where a number of different distributions exist within a sample. A sample of patients in a trial may include patients with disease of varying degrees of aggressiveness driven by genetic factors associated with the disease, and therefore different exponential, Weibull, or lognormal distributions may exist within the data. Accordingly, the use of spline-based models is a relatively simple method of modelling complex survival data.

In summary, the following parametric functions were explored as part of the survival analysis for PFS:

- Unstratified (with treatment as an indicator variable) exponential, Weibull, Gompertz, lognormal, loglogistic, generalised gamma and gamma
- Stratified Weibull, Gompertz, lognormal, loglogistic, gen-gamma and gamma
- Unstratified and stratified spline models, with one, two and three knots

Internal validity of PFS parametric survival functions

The model fit statistics (Akaike information criterion and Bayesian information criterion) for the parametric survival functions explored for PFS for selpercatinib and the reference arm are presented in Table 40. Visual assessment of the parametric survival functions to the Kaplan-Meier data for selpercatinib and the reference arm was assessed through the extrapolations presented in Figure 20 and Figure 21, respectively.

Table 40: Model fit statistics for PFS parametric survival functions for selpercatinib and reference arm (pemetrexed + platinum chemotherapy)

Function	PFS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	540.7	546.4	12	3
Weibull	540.2	548.8	11	6
Generalised gamma	538.1	549.5	7	8
Lognormal	536.4	544.9	3	2
Loglogistic	536.3	544.9	2	1
Gompertz	542.6	551.2	17	10
Gamma	539.1	547.6	8	4
Spline/Knot=1	539.3	550.7	9	9
Spline/Knot=2	541.1	555.4	14	14
Spline/Knot=3	536.1	553.2	1	12
Stratified Weibull	542.2	553.6	16	13
Stratified generalised gamma	539.9	557.0	10	16
Stratified Lognormal	536.6	548.0	4	5
Stratified Llogistic	537.6	549.0	6	7
Stratified Gompertz	544.6	556.0	19	15
Stratified Gamma	541.0	552.4	13	11
Stratified Spline/Knot=1	542.1	559.2	15	17
Stratified Spline/Knot=2	544.1	566.9	18	19
Stratified Spline/Knot=3	537.6	566.1	5	18

Footnotes: AIC and BIC statistics represent reflect the model fit to both arms.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival.

Figure 20: Selpercatinib PFS parametric survival function extrapolations

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Figure 21: Pemetrexed plus platinum chemotherapy (reference arm) PFS parametric survival function extrapolations

Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

According to AIC/BIC statistics, all survival functions have similar fits to the observed Kaplan-Meier data for both the selpercatinib and reference arm. This was also reflected in the visual assessment of the fit of functions to the (observed) Kaplan-Meier data, which all appeared to provide a similar fit to both arms.

As is typical, slight differences in the best statistically fitting curves between AIC and BIC are present, owing to the fact that BIC statistics explore both the number of parameters as well as the fit of the curve. In contrast, AIC statistics focus on the fit of the curve alone. As a result, survival curves which include a higher number of parameters, such as the generalised gamma curve (three-parameter distribution), provide more favourable AIC results compared to BIC. Survival curves which only include one parameter, such as the exponential, typically have similar AIC and BIC results.

Owing to the similarity in values in AIC/BIC statistics, it was not possible to specify an optimal curve choice. Furthermore, AIC/BIC statistics only provide information on the goodness of fit of the survival curve to the observed Kaplan-Meier data and do not provide information on the validity of the curves beyond the follow-up time of the trial data. As such, the external validity of the survival curves was an important consideration when selecting the most appropriate survival curve.

Due to the lack of availability of long-term data for *RET* targeted therapies, clinical feedback was sought from UK-based expert oncologists on the long-term clinical validity of the survival curves.[17] The expert oncologists provided landmark estimates for PFS at 3, 5, 10 and 20 years as well as an estimate for median PFS for selpercatinib and the relevant comparators. These values were then compared to the survival curves for PFS (see Table 41 below).

Table 41: Survival curves landmark PFS estimates compared to clinical expert values

Survival curves	Selpercatinib					Pemetrexed plus platinum chemotherapy					Pembrolizumab combination therapy[a]				
	Median PFS (mts)	Survival (%)				Median PFS (mts)	Survival (%)				Median PFS (mts)	Survival (%)			
		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year
Exponential	[redacted]	37.08	19.14	3.66	0.13	[redacted]	0.81	0.03	0.00	0.00	[redacted]	8.26	1.57	0.02	0.00
Weibull	[redacted]	33.03	13.29	1.05	0.00	[redacted]	0.17	0.00	0.00	0.00	[redacted]	3.72	0.25	0.00	0.00
Generalised gamma	[redacted]	34.02	18.38	5.56	1.02	[redacted]	2.80	0.70	0.06	0.00	[redacted]	N/A	N/A	N/A	N/A
Lognormal	[redacted]	34.35	19.80	7.30	1.98	[redacted]	4.33	1.54	0.28	0.04	[redacted]	N/A	N/A	N/A	N/A
Loglogistic	[redacted]	33.56	18.78	7.42	2.70	[redacted]	4.67	2.19	0.77	0.27	[redacted]	N/A	N/A	N/A	N/A
Gompertz	[redacted]	35.20	15.15	0.95	0.00	[redacted]	0.51	0.01	0.00	0.00	[redacted]	6.50	0.72	0.00	0.00
Gamma	[redacted]	32.45	13.21	1.25	0.01	[redacted]	0.26	0.00	0.00	0.00	[redacted]	N/A	N/A	N/A	N/A
Spline knot 1	[redacted]	38.57	21.86	5.68	0.45	[redacted]	0.90	0.05	0.00	0.00	[redacted]	8.70	2.03	0.06	0.00
Spline knot 2	[redacted]	39.69	23.86	7.44	0.90	[redacted]	1.11	0.09	0.00	0.00	[redacted]	9.72	2.69	0.14	0.00
Spline knot 3	[redacted]	42.14	28.96	13.26	3.71	[redacted]	1.39	0.22	0.00	0.00	[redacted]	10.89	4.16	0.56	0.02
Stratified Weibull	[redacted]	33.30	13.66	1.16	0.00	[redacted]	0.16	0.00	0.00	0.00	[redacted]	3.60	0.23	0.00	0.00
Stratified Generalised gamma	[redacted]	39.93	26.62	13.16	5.41	[redacted]	3.26	1.07	0.18	0.02	[redacted]	N/A	N/A	N/A	N/A
Stratified Lognormal	[redacted]	39.33	25.59	11.92	4.44	[redacted]	2.82	0.82	0.11	0.01	[redacted]	N/A	N/A	N/A	N/A
Stratified Loglogistic	[redacted]	36.55	22.18	9.89	4.05	[redacted]	3.86	1.72	0.56	0.18	[redacted]	N/A	N/A	N/A	N/A
Stratified Gompertz	[redacted]	34.95	14.55	0.71	0.00	[redacted]	0.64	0.02	0.00	0.00	[redacted]	7.32	1.07	0.00	0.00

Stratified Gamma	[redacted]	33.46	14.39	1.61	0.02	[redacted]	0.22	0.00	0.00	0.00	[redacted]	N/A	N/A	N/A	N/A
Stratified Spline Knot 1	[redacted]	35.11	16.43	2.27	0.04	[redacted]	3.84	1.10	0.09	0.00	[redacted]	18.46	9.63	2.63	0.35
Stratified Spline Knot 2	[redacted]	36.13	18.21	3.26	0.10	[redacted]	16.44	15.30	13.83	12.43	[redacted]	39.22	37.80	35.86	33.93
Stratified Spline Knot 3	[redacted]	37.46	20.95	5.31	0.40	[redacted]	31.18	40.56	52.85	63.71	[redacted]	54.66	62.64	71.85	79.16
Expert opinion	21	30-35	15	3-5	1-5	6-11	15	<5-5	0-<1	0-<1	10-11	15	<5-5	0-<1	0-<1

Footnote: [a] Estimates were not obtained for parametric survival functions for pembrolizumab combination therapy where the proportional hazards assumption does not apply (stratified and unstratified generalised gamma, lognormal and loglogistic).
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; mts: months; N/A: not applicable; NR: not reported; PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on file. Clinical validation meeting minutes.[17]

The Gompertz distribution was selected as the base case survival curve for PFS (all treatment arms), as informed by the following factors.

Firstly, the landmark estimates generated when using the Gompertz distribution aligned well with those provided for selpercatinib by the clinical experts, as presented in Table 41. A comparison of predicted survival estimates for selpercatinib was also made with trial data for an analogous targeted therapy in untreated advanced NSCLC. One of the clinical experts consulted advised that survival estimates for selpercatinib in *RET* fusion-positive patients could be deemed comparable to those of *ALK*-positive patients treated with targeted therapies.[17] Two such therapies are brigantinib and alectinib, which were assessed in the ALTA-1L and ALEX trials, respectively.[107, 108] Median PFS for these two therapies was found to be 24.02 and 34.8 months, respectively. The median PFS estimated for selpercatinib with the Gompertz curve was [redacted] months which compares to more conservative benchmark estimates from trials in other targeted therapies. Further to the above, the Gompertz distribution is associated with a short tail, and feedback from clinical experts obtained in the pre-treated submission for selpercatinib (TA760)[12] was that targeted therapies are not anticipated to be associated with a long tail.

The proportional hazards assumption did not hold for PFS and therefore treatment-specific curves were explored in scenario analyses. However, with the overall uncertainty from unanchored ITCs and most trials meeting the proportional hazard (PH) assumptions, it was deemed acceptable to apply the PH assumption in the base case.

The Gompertz distribution also provided good external validity for the pemetrexed plus platinum-based chemotherapy and pembrolizumab combination arms, with the modelled median PFS for each generally aligning to the results of the KEYNOTE-189 trial (4.9 and 9.0 months, respectively).[109] It is noted however that the KEYNOTE-189 trial did not comprise a cohort *RET* fusion-positive patients and also included patient cross-over between arms.

Alternative curves that may produce clinically plausible survival estimates where the proportional hazards assumption holds were explored in scenario analyses. These included the exponential, Weibull, stratified Weibull, stratified Gompertz and stratified spline knot 1 (see Section B.3.10.3). In addition, a scenario was explored where the proportional hazards assumption was relaxed and the spline-knot 3 was explored for the pemetrexed plus platinum and pembrolizumab combination therapy arms.

B.3.2.3 Overall survival

As with PFS, in order to inform long-term estimates of OS in the model for selpercatinib and comparators, it was necessary to extrapolate the OS data generated for selpercatinib and the reference arm (pemetrexed plus platinum chemotherapy) through the application of parametric survival functions. OS functions for pembrolizumab combination therapy were then constructed through the application of an HR to the reference arm extrapolation (Table 42), as generated through the NMA described in Section B.2.8.2.

Table 42: OS HRs applied to reference arm (pemetrexed + platinum chemotherapy)

Drug (Patient subgroup)	HR (95% CrI)
Pembrolizumab + pemetrexed + platinum chemotherapy	[redacted]

Abbreviations: CrI: Credible interval; HR: hazard ratio; OS: overall survival.

The approach to parametric survival curve selection mirrored that of PFS; the recommendations of NICE Decision Support Unit (DSU) TSD 14 were followed.[92] Stratified spline knot models were not considered for OS as the models did not coverage. The following set of curves were explored for selpercatinib and the reference arm (and consequently the pembrolizumab combination therapy arm):

- Unstratified (with treatment as an indicator variable) exponential, Weibull, Gompertz, lognormal, loglogistic, gen-gamma and gamma
- Stratified Weibull, Gompertz, lognormal, loglogistic, gen-gamma and gamma
- Unstratified spline models, with one, two and three knots

Internal validity of OS parametric survival functions

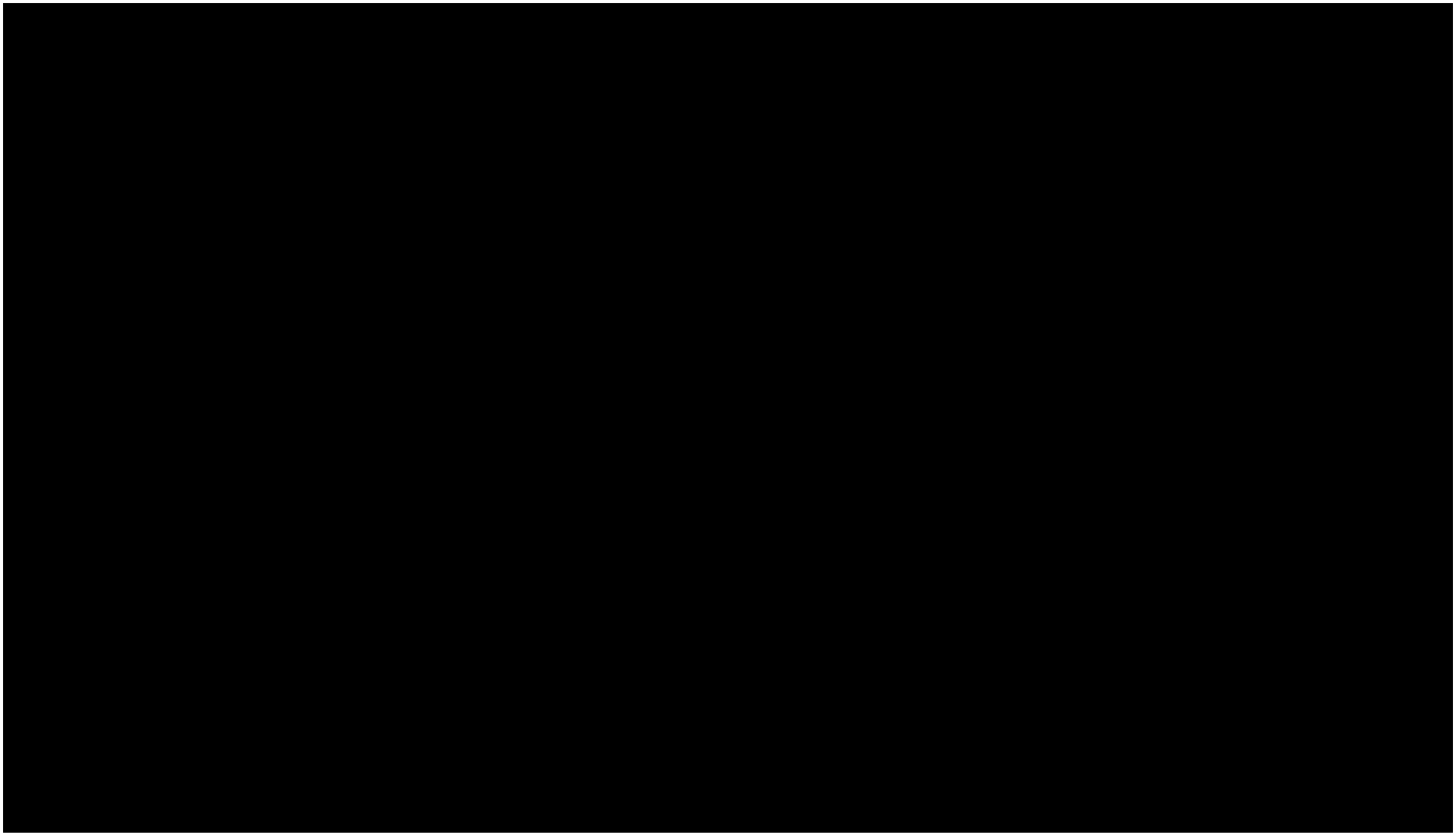
The model fit statistics for the parametric survival functions explored for selpercatinib and the reference arm for OS are presented in Table 43. Visual assessment of the parametric survival functions to the Kaplan-Meier data for selpercatinib and the reference arm was assessed through the extrapolations presented in Figure 22 and Figure 23 for OS.

Table 43: Model fit statistics for OS parametric survival functions for selpercatinib and reference arm (pemetrexed + platinum chemotherapy)

Function	OS			
	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	451.6	457.3	9	3
Weibull	450.4	458.9	7	5
Generalised gamma	449.4	460.8	4	7
Lognormal	447.5	456.0	1	1
Loglogistic	448.0	456.6	2	2
Gompertz	452.3	460.9	14	8
Gamma	449.6	458.1	5	4
Spline/Knot=1	451.6	463.1	10	11
Spline/Knot=2	451.7	466.0	11	14
Spline/Knot=3	452.8	469.9	15	16
Stratified Weibull	451.9	463.3	12	12
Stratified Generalised gamma	452.3	469.4	13	15
Stratified Lognormal	449.4	460.8	3	6
Stratified Llogistic	449.9	461.3	6	9
Stratified Gompertz	454.1	465.5	16	13
Stratified Gamma	451.3	462.7	8	10

Footnotes: AIC and BIC statistics represent reflect the model fit to both arms.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: progression-free survival.

Figure 22: Selpercatinib OS parametric survival function extrapolations



Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Figure 23: Pemetrexed plus platinum chemotherapy (reference arm) OS parametric survival function extrapolations

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

According to AIC/BIC statistics, all survival functions have similar fits to the observed Kaplan-Meier data for both the selpercatinib and reference arm. This was reflected in the visual assessment of the fit of function to the (observed) Kaplan-Meier data, which all appeared to provide a similar fit to both arms.

External validity of OS parametric survival functions

As with PFS, owing to the similarity in values in AIC/BIC statistics, it was not possible to specify an optimal curve choice. In addition, owing to the small number of OS events in LIBRETTO-001, the external validity of the survival curves was particularly important when selecting the most appropriate survival curve. Accordingly, clinical feedback was sought from UK based expert oncologists on the external validity of the survival curves.[17] The expert oncologists provided landmark estimates for OS at 3, 5, 10 and 20 years as well as an estimate for median OS for selpercatinib and relevant comparators. These values were then compared to the survival curves for OS (Table 44).

Table 44: Survival curves landmark OS estimates compared to clinical expert values

Survival curves	Selpercatinib					Pemetrexed plus platinum chemotherapy					Pembrolizumab combination therapy				
	Median OS (mts)	Survival (%)				Median OS (mts)	Survival (%)				Median OS (mts)	Survival (%)			
		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year
Exponential	[redacted]	61.97	45.05	20.29	4.12	[redacted]	13.36	3.49	0.12	0.00	[redacted]	29.33	12.95	1.68	0.03
Weibull	[redacted]	58.67	36.16	8.69	0.28	[redacted]	6.38	0.53	0.00	0.00	[redacted]	18.70	4.08	0.05	0.00
Generalised gamma	[redacted]	59.79	42.53	21.49	8.05	[redacted]	17.03	8.00	2.12	0.39	[redacted]	N/A	N/A	N/A	N/A
Lognormal	[redacted]	59.87	43.07	22.65	9.24	[redacted]	18.16	9.11	2.81	0.65	[redacted]	N/A	N/A	N/A	N/A
Loglogistic	[redacted]	58.90	40.01	19.11	7.72	[redacted]	15.57	7.90	2.95	1.07	[redacted]	N/A	N/A	N/A	N/A
Gompertz	[redacted]	57.55	26.92	0.08	0.00	[redacted]	6.12	0.13	0.00	0.00	[redacted]	18.23	1.76	0.00	0.00
Gamma	[redacted]	58.50	36.44	10.00	0.63	[redacted]	7.47	0.97	0.00	0.00	[redacted]	N/A	N/A	N/A	N/A
Spline Knot 1	[redacted]	60.68	41.88	15.74	1.97	[redacted]	9.46	1.64	0.02	0.00	[redacted]	23.77	8.18	0.49	0.00
Spline Knot 2	[redacted]	57.11	31.14	4.26	0.02	[redacted]	5.45	0.23	0.00	0.00	[redacted]	16.98	2.49	0.00	0.00
Spline Knot 3	[redacted]	59.22	37.83	10.54	0.55	[redacted]	7.24	0.77	0.00	0.00	[redacted]	20.19	5.14	0.10	0.00
Stratified Weibull	[redacted]	56.63	30.66	4.11	0.02	[redacted]	8.00	0.97	0.00	0.00	[redacted]	21.46	5.92	0.16	0.00
Stratified Generalised Gamma	[redacted]	60.95	44.28	23.69	9.88	[redacted]	17.72	8.65	2.53	0.54	[redacted]	N/A	N/A	N/A	N/A
Stratified Lognormal	[redacted]	60.52	44.21	24.04	10.30	[redacted]	17.58	8.64	2.57	0.56	[redacted]	N/A	N/A	N/A	N/A
Stratified Loglogistic	[redacted]	57.66	37.57	16.58	6.16	[redacted]	16.47	8.59	3.33	1.24	[redacted]	N/A	N/A	N/A	N/A
Stratified Gompertz	[redacted]	56.25	21.65	0.00	0.00	[redacted]	11.06	1.80	0.00	0.00	[redacted]	26.14	8.65	0.20	0.00

Stratified Gamma	[redacted]	57.19	33.47	7.46	0.29	[redacted]	8.44	1.27	0.01	0.00	[redacted]	N/A	N/A	N/A	N/A
Clinical Experts	50-72	60	45-50	20	1-10	12 to 24	25-40	6-17	<1-5	0-<1	12 to 24	25-40	6-17	<1-5	0-<1

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; mts: months; N/A: not applicable; NR: not reported; PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on file. Clinical validation meeting minutes.[17]

The spline knot 1 distribution was selected as the base case survival curve for OS (all treatment arms), as informed by the following factors.

The landmark estimates generated when using the spline knot 1 model were generally consistent with those provided by the expert oncologists for selpercatinib (Table 44). The predicted long-term landmark rates were within the range given by the clinical experts (1–10%). In addition, the modelled median OS for selpercatinib was consistent with a real-world evidence study (Tan *et al.* 2020)[52] evaluating OS in a population of *RET* fusion-positive NSCLC patients treated with a selective *RET* tyrosine kinase inhibitor ([redacted] vs 49.3 months, respectively). The estimates for selpercatinib with the spline knot 1 function also aligned well with those for the *ALK-1* inhibitor alectinib (48.2 months).[110]

As with PFS, the same curve choice was applied to the pemetrexed plus platinum based chemotherapy arm. The HR from the NMA (Section B.2.8) was then applied to generate the OS extrapolation for pembrolizumab combination therapy.

The landmark estimates generated when using the spline knot 1 model were generally consistent with those provided by the expert oncologists for the two comparator therapies (Table 44). Furthermore, the spline knot 1 model provided good external validity versus trial data, with the modelled median OS for each comparator aligning approximately to the results of the KEYNOTE-189 trial (22.0 and 10.6 months for the pembrolizumab combination and pemetrexed plus platinum-based chemotherapy arms, respectively).[109] However, it is acknowledged that the predicted long-term landmark rates may be conservative for the pembrolizumab combination arm. The KEYNOTE-189 trial included patient cross-over between arms which was anticipated to result in less conservative estimates for the pemetrexed plus platinum based chemotherapy arm, hence making the HR from the NMA applied to generate the OS extrapolation for pembrolizumab combination therapy arm a more conservative estimate. Scenario analyses whereby alternative curves for the comparator arms which predict higher long-term landmark rates were therefore explored. It is also noted that the KEYNOTE-189 trial did not comprise a cohort *RET* fusion-positive patients, however as stated in Section B.1.2.1 the prognostic impact of *RET* fusion is inconclusive.

Alternative curves that may produce clinically plausible survival estimates where the proportional hazards assumption holds were explored in scenario analyses. These included the Exponential, and spline knot 3. In addition, as the proportional hazards assumption did not hold as strongly for OS as it did for PFS (see Section B.2.8), scenario analyses were performed where the proportional hazards assumption was relaxed by applying alternative curves to the comparator arms compared to the base case curve for selpercatinib (exponential for the comparator arms).

Base case parametric curve selections

Table 45: Selected base case survival functions for PFS and OS

	Selpercatinib	Reference arm (pemetrexed + platinum chemotherapy)	Pembrolizumab combination therapy
Base case PFS extrapolation	Gompertz	Gompertz	Gompertz
Base case OS extrapolation	Spline knot 1	Spline knot 1	Spline knot 1

Abbreviations: OS: overall survival; PFS: progression-free survival.

The parametric survival curves for PFS and OS selected for the base case are presented in Figure 24 and Figure 25, respectively.

Figure 24: PFS parametric survival extrapolations selected for the base case

Abbreviations: pem+plat: pemetrexed plus platinum chemotherapy; pembro: pembrolizumab; PFS: progression free survival.

Figure 25: OS parametric survival extrapolations selected for the base case

Abbreviations: pem+plat: pemetrexed plus platinum chemotherapy; pembro: pembrolizumab; PFS: progression free survival.

B.3.2.4 Time to treatment discontinuation

In line with the methodology taken for PFS and OS, a range of standard parametric distributions were explored to extrapolate time to treatment discontinuation (TTD) data from the LIBRETTO-001 trial. This was conducted to estimate duration of treatment for selpercatinib in the model. Conservatively, treatment discontinuation for comparators was modelled using the PFS curve for the intervention, capped at a maximum number of cycles where specified in the SmPC. Statistical fit results for TTD are presented in Table 46.

Table 46: Time-to-treatment discontinuation model evaluation results for the selpercatinib in treatment-naïve *RET* fusion-positive NSCLC

	TTD			
Function	**AIC**	**BIC**	**Rank (AIC)**	**Rank (BIC)**
Exponential	310.9	313.0	1	1
Weibull	312.7	317.0	3	3
Generalised gamma	314.1	320.5	5	6
Lognormal	317.4	321.7	9	8
Llogistic	314.5	318.8	7	5
Gompertz	312.3	316.6	2	2
Gamma	312.8	317.1	4	4
Spline/Knot=1	314.1	320.6	6	7
Spline/Knot=2	316.1	324.7	8	9
Spline/Knot=3	317.8	328.6	10	10

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; NSCLC: non–small cell lung cancer; *RET*: Rearranged during Transfection; TTD: time to treatment discontinuation.

According to AIC/BIC statistics, all survival functions have similar fits to the observed Kaplan-Meier data for selpercatinib. This was reflected in the visual assessment of the fit of functions to the (observed) Kaplan-Meier data from LIBRETTO-001 (Figure 26).

Figure 26: Selpercatinib TTD parametric survival function extrapolations

Abbreviations: KM: Kaplan-Meier; TTD: time to treatment discontinuation.

The landmark predictions from the top 10 best fitting curves for TTD are presented in Table 47.

Table 47: Top 10 best statistically fitting AIC/BIC curves landmark TTD estimates

Survival curves	Selpercatinib				
	Median TTD (mts)	Survival (%)			
		3 year	5 year	10 year	20 year
Exponential	23.93	35.36	17.68	3.13	0.10
Weibull	23.70	34.20	15.76	2.10	0.03
Generalised gamma	24.16	31.07	6.61	0.00	0.00
Lognormal	24.85	40.68	28.59	15.56	7.21
Loglogistic	24.39	38.27	24.75	12.22	5.56
Gompertz	23.93	31.79	9.59	0.03	0.00
Gamma	23.70	34.70	16.68	2.62	0.06
Spline Knot 1	23.70	32.35	12.54	0.87	0.00
Spline Knot 2	23.70	32.72	13.30	1.11	0.00
Spline Knot 3	24.16	31.82	10.84	0.43	0.00

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; mts: months; TTD: time to discontinuation.

Feedback from expert oncologists consulted as part of the appraisal process noted that patients who progress are often kept on treatment until they have received a further two scans, delivered approximately 3 months apart. It was however highlighted that if substantial disease progression occurs patients will quickly change treatment.[17] Evidence for patients remaining on treatment post progression is supported by data from the LIBRETTO-001 trial, as the mean time to treatment discontinuation post-progression was [redacted] days (Table 48).

Table 48: LIBRETTO-001 time from progression to treatment discontinuation

Mean (days)	SE (days)	SD (days)	N
[redacted]	[redacted]	[redacted]	69

Abbreviations: SE: standard error; SD: standard deviations.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 (15th June 2021 cut-off).[80]

An exponential curve was selected for the base case for TTD for selpercatinib. The exponential was the best fitting curve, as informed by AIC and BIC, and was deemed clinically plausible as it lies above the PFS landmark estimates, which is in line with feedback received from clinical expert oncologists that a proportion of patients stay on treatment post-progression for a short period of time. Owing to their high AIC and BIC ranking, the Gompertz, Weibull and gamma survival curves were explored in scenario analyses (see Section B.3.10.3).

The parametric survival curve for TTD for selpercatinib selected for the base case is presented in Figure 27.

Figure 27: TTD parametric survival extrapolation selected for the base case overlaid on the base case extrapolation for PFS

Abbreviations: TTD: time to treatment discontinuation.

B.3.2.5 Adverse events

Probabilities of individual AEs for each intervention were based on trial data. In order to focus on AEs which are likely to have an important impact on costs or HRQoL, all Grade 3–4 adverse events with at least 2% difference in frequency between interventions in the source trials were included. Costs and utility decrements (if any) associated with each AE were included in the model, see Section B.3.3.4 and Section B.3.4.3, respectively. The incidence of Grade 3–4 adverse events included in the model for selpercatinib and comparators are reported in Table 49.

Table 49: Incidence of Grade 3–4 adverse events for selpercatinib and relevant comparators included in the model

Adverse Event	Selpercatinib (N = 69)	Pembrolizumab + pemetrexed + platinum chemotherapy (N = 405)	Pemetrexed + platinum chemotherapy (N = 202)
Diarrhoea	[redacted]	5.19%	2.97%
Hypertension	[redacted]	0.49%	0.00%
ECG QT prolonged	[redacted]	0.00%	0.00%
Abdominal pain	[redacted]	0.00%	0.00%
Haemorrhage	[redacted]	0.00%	0.00%
Fatigue	[redacted]	5.68%	2.48%
Decreased appetite	[redacted]	1.48%	0.50%
Rash	[redacted]	0.00%	0.00%
Asthenia	[redacted]	6.17%	3.47%
Vomiting	[redacted]	3.70%	2.97%
Dyspnoea	[redacted]	3.70%	5.45%
Alanine aminotransferase increased	[redacted]	0.00%	0.99%
Aspartate aminotransferase increased	[redacted]	0.00%	0.00%
Hyponatraemia	[redacted]	0.25%	0.99%
Lymphopenia	[redacted]	0.00%	0.00%
Pneumonia	[redacted]	5.68%	8.42%
Dehydration	[redacted]	1.23%	0.99%
Thrombocytopenia	[redacted]	7.90%	6.93%
Neutropenia	[redacted]	15.80%	11.88%
Anaemia	[redacted]	16.30%	15.35%
Pleural effusion	[redacted]	1.48%	1.98%
Febrile neutropenia	[redacted]	5.68%	1.98%
Pyrexia	[redacted]	0.00%	0.00%
Pneumonitis	[redacted]	2.96%	1.98%
Nausea	[redacted]	3.46%	3.47%

Adverse Event	Selpercatinib (N = 69)	Pembrolizumab + pemetrexed + platinum chemotherapy (N = 405)	Pemetrexed + platinum chemotherapy (N = 202)
Hepatitis Lab abnormalities	[redacted]	1.48%	0.00%
Hypothyroidism	[redacted]	0.00%	0.00%
Hyperthyroidism	[redacted]	0.00%	0.00%
Cellulitis	[redacted]	0.00%	0.00%
Sepsis[a]	[redacted]	0.00%	0.00%
Acute kidney injury[a]	[redacted]	0.00%	0.00%
Chronic obstructive pulmonary disease	[redacted]	0.99%	1.49%
Colitis	[redacted]	0.00%	0.00%
Urinary tract infection	[redacted]	0.00%	0.00%
Peripheral neuropathy	[redacted]	0.00%	0.00%
Decreased platelet count	[redacted]	0.25%	0.00%
Decreased neutrophil count	[redacted]	0.00%	0.00%
Severe skin reaction	[redacted]	0.00%	0.00%
Proteinuria	[redacted]	0.00%	0.00%
Source	LIBRETTO-001	KEYNOTE-189[a]	KEYNOTE-189[a]

Footnotes: [a]The model includes AE data from alternative trials included in the NMA (KEYNOTE-189 for pembrolizumab pemetrexed and carboplatin).[111] Certain AEs are included because of their incidence in these trials (not presented in the table).
Abbreviations: AE: adverse event; ECG: electrocardiogram; NMA: network meta-analysis; NSCLC: non–small cell lung cancer; *RET*: Rearranged during transfection.
Sources: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off);[80] KEYNOTE-021;[105, 112] KEYNOTE-189.[86]

B.3.3 Measurement and valuation of health effects

B.3.3.1 Health-related quality-of-life data from clinical trials

EORTC QLQ-C30 data were collected in the LIBRETTO-001 study, as described in Section B.2.5.5. The questionnaires were to be answered by the subject to the best of their ability, prior to receiving drug on the first day of treatment, every second cycle in the first year followed by every third cycle from cycle 13, and at the post-discontinuation follow-up visit. The same questionnaire was completed by patients who discontinued treatment due to disease progression.

No EQ-5D data were collected in LIBRETTO-001.

B.3.3.2 Mapping

As no EQ-5D data were collected during the LIBRETTO-001 trial, various methods were explored to map the EORTC QLQ-C30 data to EQ-5D-3L.

Mapping techniques typically used in NSCLC models including Kontodimopulos *et al.* 2009[113] (ordinary least square regression), Marriott *et al.* 2017[114] (linear mixed regression), Rowen *et al.* 2011[115] (response mapping) and Young *et al.* 2015[93] (response mapping) were explored. The results of the different mapping algorithms are presented in Table 50 below.

EQ-5D-3L results generated using the mapping algorithm outlined by Young *et al.* (2015) produced the most plausible and lowest utility estimates, and were therefore conservatively chosen for the base case. As such, EORTC QLQ-C30 data collected during the LIBRETTO-001 trial, mapped to EQ-5D data using the algorithm presented in Young *et al.* (2015), were utilised in the base case analysis for both the PF and PD health states.

Table 50: Mapping algorithms explored to convert the EORTC-QLQ-C30 data obtained from LIBRETTO-001 trial to EQ-5D-3L

Mapping technique	Mapped EQ-5D-3L values			
	PF		PD	
	Mean (SD)	CI	Mean (SD)	CI
Kontodimopoulos 2009[113]	[redacted]	[redacted]	[redacted]	[redacted]
Marriott 2017[114]	[redacted]	[redacted]	[redacted]	[redacted]
Rowen 2011[89]	[redacted]	[redacted]	[redacted]	[redacted]
Young 2015[93]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; PD: progressed disease; PF: progression free; SD: standard deviation.

B.3.3.3 Health-related quality-of-life studies

Utility values included in the model were derived from values obtained from the LIBRETTO-001 trial, mapped to EQ-5D data using the algorithm presented in Young *et al.* (2015).[93] Therefore, no further extraction of HRQoL studies from the SLR to identify cost-effectiveness studies was performed.

B.3.3.4 Adverse reactions

It is well accepted that adverse events have a negative impact on patients' HRQoL. Several studies have been performed exploring the negative impact of adverse events associated with cancer treatment, as discussed in Section B.1.3.1. As such, disutility values were applied to those experiencing adverse events to estimate the reduction in HRQoL due to the event for its duration. All adverse reactions were assumed to occur in the first cycle of the model and last for a specified duration. This is in line with previous cost-effectiveness analyses in NSCLC.

Utility decrements for adverse events and associated duration were based on values from previous NICE technology appraisals. Decrements, duration and QALY losses for each adverse event as applied in the model are presented in Table 51.

Table 51: Adverse event disutility decrements applied in the cost-effectiveness model

Adverse event	Decrement	Duration (days)	QALY loss	Source
Diarrhoea	-0.047	5.5	-0.0007	NICE TA621; Disutility: Nafees et al., 2008; Duration: NICE TA476 (Study CA046)
Hypertension	-0.085	15.0	-0.0035	NICE TA428; Disutility: KEYNOTE-010 (TA428); Duration: Assumption
ECG QT prolonged	0.000	0.0	0.0000	Assumption
Fatigue	-0.074	23.8	-0.0048	NICE TA621; Disutility: Nafees et al., 2008; Duration: NICE TA306 (PIX301), NICE TA476 (Study CA046)
Decreased appetite	-0.085	15.0	-0.0035	NICE TA428; Disutility: KEYNOTE-010 (TA428); Duration: Assumption
Asthenia	-0.074	23.8	-0.0048	NICE TA484; Disutility: Nafees et al., 2008; Duration: Assumption (same as fatigue)
Vomiting	-0.085	15.0	-0.0035	NICE TA428; Disutility: KEYNOTE-010 (TA428); Duration: Assumption
Dyspnoea	-0.050	15.0	-0.0021	NICE TA484; Disutility: Doyle et al., 2008; Duration: Assumption
Alanine aminotransferase increased	-0.051	14.7	-0.0020	NICE TA621; Disutility and Duration: Assumption (average of other disutilities)
Aspartate aminotransferase increased	-0.051	14.7	-0.0020	NICE TA621; Disutility and Duration: Assumption (average of other disutilities)
Hyponatraemia	-0.085	15.0	-0.0035	NICE TA428; Disutility: KEYNOTE-010 (TA428); Duration: Assumption
Lymphopenia	-0.050	15.0	-0.0021	NICE TA484; Disutility: TA449; Duration: Assumption
Pneumonia	-0.008	15.0	-0.0003	NICE TA484; Disutility: Marti et al., 2013; Duration: Assumption
Thrombocytopenia	0.000	0.0	0.0000	Assumption
Neutropenia	-0.090	15.0	-0.0037	NICE TA428, Table 10; Disutility: Nafees et al., 2008; Duration: Assumption
Anaemia	-0.073	23.8	-0.0048	NICE TA484; Disutility: Nafees et al., 2008; Duration: Assumed same as fatigue
Pleural effusion	-0.085	15.0	-0.0035	NICE TA428; Disutility: KEYNOTE-010 (TA428); Duration: Assumption
Febrile neutropenia	-0.090	15.0	-0.0037	NICE TA428, Table 10; Disutility: Nafees et al., 2008; Duration: Assumption

Pneumonitis	-0.085	15.0	-0.0035	NICE TA428; Disutility: KEYNOTE-010 (TA428); Duration: Assumption
Nausea	-0.085	15.0	-0.0035	NICE TA428; Disutility: KEYNOTE-010 (TA428); Duration: Assumption
Hepatitis Lab abnormalities	0.000	0.0	0.0000	Assumption
Sepsis	0.000	15.0	0.0000	Assumed same as Febrile Neutropenia
Acute kidney injury	0.000	0.0	0.0000	NICE TA428; Disutility: KEYNOTE-010 (TA428); Duration: Assumption
Chronic obstructive pulmonary disease	-0.085	15.0	-0.0035	NICE TA428; Disutility: KEYNOTE-010 (TA428); Duration: Assumption
Urinary tract infection	0.000	0.0	0.0000	NICE TA428; Disutility: KEYNOTE-010 (TA428); Duration: Assumption
Peripheral neuropathy	-0.085	15.0	-0.0035	NICE TA428; Disutility: KEYNOTE-010 (TA428); Duration: Assumption
Decreased platelet count	0.000	0.0	0.0000	Assumption
Decreased neutrophil count	0.000	0.0	0.0000	Assumption
Severe skin reaction	0.000	0.0	0.0000	Assumption
Proteinuria	0.000	0.0	0.0000	Assumption

Abbreviations: ECG: electrocardiogram; QALY: quality-adjusted life year; NICE: National Institute for Health and Care Excellence.
Source: Doyle et al., 2008;[116] KEYNOTE-010 (TA428);[117] Marti et al., 2013;[118] Nafees et al., 2008;[119] NICE TA306;[120] NICE TA428;[121] NICE TA476;[122]; NICE TA484;[100] NICE TA654.[98]

B.3.3.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Utility values were applied to the progression-free and progressed health states to estimate HRQoL. As most responses to treatment with selpercatinib reported in the LIBRETTO-001 trial were partial responses, it was deemed unlikely that there would be an important improvement in HRQoL for responders. Therefore, no adjustment to the progression-free utility weight was made to reflect response in the base case.

Utility values were derived from EORTC QLQ-C30 data from the LIBRETTO-001 trial mapped to EQ-5D-3L values using the methods outline by Young *et al.* (2015).[93] A summary of the utility values used for the base case analysis is presented in Table 52.

A scenario analyses was explored in which HSUVs were assumed to align with those accepted for TA654 for osimertinib in untreated EGFR mutation-positive NSCLC and for TA812 for pralsetinib for treating *RET* fusion-positive advanced NSCLC[18], which elicited HSUVs directly from clinical trial data. The values accepted by the Committee were considered a suitable proxy for selpercatinib, being another targeted treatment in non-squamous NSCLC.[98] The utility values used in the scenario case analysis are presented in Table 53.

Table 52: Utility estimates used in the base case analysis

Health state	Value	Source
PF	[redacted]	LIBRETTO-001[80]
PD	[redacted]	LIBRETTO-001[80]

Abbreviations: PD: progressed disease; PF: progression-free.
Source: Eli Lilly. Data on File. LIBRETTO-001.[80]

Table 53: Utility estimates used in the scenario analysis

Health state	Value	Source	Justification
PF	0.794	TA654	Data elicited directly from trials for patients for EGFR mutations on targeted treatment with osimertinib.
PD	0.678	TA654	PD values elicited from AURA2 for a ≥second line population which matches the impact of subsequent treatments on utility

Abbreviations: PD: progressed disease; PF: progression-free; TA: technology assessment; EGFR: epidermal growth factor receptor.
Source: TA654.[98]

B.3.4 Cost and healthcare resource use identification, measurement and valuation

Values for cost and resource use included in the model were based on a targeted literature review of relevant technology appraisals that had been previously accepted by NICE. Therefore, no further extraction of studies from the SLR to identify cost-effectiveness studies was performed.

The following cost and resource use categories were captured in the analysis:

- Section B.3.3.1: Drug acquisition, administration and monitoring
- Section B.3.4.1: Subsequent treatments
- Section B.3.4.2: Medical management of the condition by health state
- Section B.3.4.3: AEs
- Section B.3.4.4: End of life (terminal care) costs

As described in Section B.3.1.2, the perspective is that of the UK NHS and PSS.

B.3.4.1 Intervention and comparators' costs and resource use

Drug acquisition costs

The price for selpercatinib is provided by Eli Lilly. Drug acquisition costs for relevant comparators were based on their list price, and all prices were extracted from the BNF or eMIT.[97, 123] Drug acquisition costs included in the cost-effectiveness analysis are presented in Table 54.

For adjusted-dose interventions a mean body weight estimate of 72.2 kg and a body surface area of 1.81 m^2 were used, as sourced from TA520 for atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy.[124]

Table 54: Drug acquisition costs for selpercatinib and relevant comparators (pembrolizumab + pemetrexed + platinum chemotherapy and pemetrexed + platinum chemotherapy)

Treatment	Form	Strength/unit	Pack size	Cost per pack (£)	Source
Selpercatinib					
Selpercatinib	Capsules	80 mg	60	[redacted]	Eli Lilly and Company. Data on file. Including PAS discount.
Selpercatinib	Capsules	40 mg	60	[redacted]	Eli Lilly and Company. Data on file. Including PAS discount.
Pembrolizumab + pemetrexed + carboplatin					
Pembrolizumab	Vial	25 mg/ml	4 ml	2,630.00	BNF (2022)
Pemetrexed	Powder	100 mg	1	128.00	BNF (2022)
Carboplatin	Vial	10 mg/ml	45 ml	6.08	eMIT (2021)
Pemetrexed + platinum chemotherapy					
Pemetrexed	Powder	100 mg	1 ml	128.00	BNF (2022)
Carboplatin	Vial	10 mg/ml	45 ml	13.51	eMIT (2021)

Abbreviations: BNF: British National Formulary; eMIT: Electronic market information tool; PAS: Patient Access Scheme.
Source: BNF (2021)[97]; eMIT (2021)[123].

For selpercatinib, a weighted average cost was applied in the model to account for dose reductions to account for toxicity control and weight based dosing. In the absence of these data for the comparators, conservatively, an RDI equivalent to that for selpercatinib from LIBRETTO-001 was applied.

In the base case, drug wastage was assumed. For IV drugs, it is assumed that unused treatment in open vials is discarded and for oral drugs the cost of whole tablets is assumed.

Drug acquisition costs are divided into treatment periods according to the dosing schedules of each treatment, as presented in Table 55. The derivation of the treatment cycle costs for selpercatinib at each dose level is provided in Table 56 –Table 58 below.

Table 55: Treatment costs included in cost effectiveness model

Treatment	Cycle length, weeks	Period 1 cost, £	Period 2 cost, £	Period 3 cost, £	Period 4 cost, £	Source
Selpercatinib (160 mg twice daily, oral)[a]	4	[redacted]	[redacted]	-	-	Dose: Draft SmPC Dose intensity: LIBRETTO-001
Pembrolizumab + pemetrexed + platinum chemotherapy[b]	3	6449.76	5507.45	5,491.98	994.68	Dose: NICE TA557; Langer *et al.* (2016) Dose intensity: assumed same as selpercatinib
Pemetrexed + platinum chemotherapy[c]	3	1189.76	1010.15	994.68	-	Dose: Doebele *et al*. (2015) Dose intensity: assumed same as selpercatinib

Notes: [a] Period 1: Week 0–3; Period 2: Week 4+ [b] Period 1: week 0–2; Period 2: week 3–11; Period 3: week 12–103; Period 4: week 104+; [c] Period 1: Week 0–2; Period 2: Week 3–17; Period 3: Week 18+.
Abbreviations: IV: intravenous; NICE: National Institute for Health and Care Excellence.
Source: NICE TA584;[71] Planchard et al., 2018;[103] Langer *et al*. (2016);[105] Doebele *et al*. (2015).[106]

Table 56. Drug acquisition costs for selpercatinib at each dose level

Regimen description	Capsule strength (mg)	Capsules per pack	Pack cost (£)	Capsule cost (£)	Capsules per dose	Doses per week	Capsules per treatment cycle[a]	Costs per treatment cycle[a] (£)
160 mg, orally, twice daily	80	60	[redacted]	[redacted]	2	14	112	[redacted]
120 mg, orally, twice daily	80	60	[redacted]	[redacted]	1	14	56	[redacted]
	40	60	[redacted]	[redacted]	1		56	[redacted]
80 mg, orally, twice daily	80	60	[redacted]	[redacted]	1	14	56	[redacted]
40 mg, orally, twice daily	40	60	[redacted]	[redacted]	1	14	56	[redacted]

[a]A treatment cycle is 4 weeks. It is assumed that a 4-week supply of drug is dispensed to patients with no disease progression at the beginning of each 4-week period.

Table 57. Weighted drug acquisition costs for selpercatinib in treatment cycle 1 (including dose reductions)

Dose	Costs per treatment cycle[a] (£)	Proportion of patients on each dose, NSCLC
160 mg, twice daily	[redacted]	[redacted]
80 mg, twice daily	[redacted]	[redacted]

[a]A treatment cycle is 4 weeks. It is assumed that a 4-week supply of drug is dispensed to patients with no disease progression at the beginning of each 4-week period.
Abbreviations: NSCLC: non-small cell lung cancer.

Table 58. Weighted drug acquisition costs for selpercatinib in treatment cycles 2+ (including dose reductions)

Dose	Costs per treatment cycle[a]	Proportion of patients on each dose, NSCLC
160 mg, twice daily	[redacted]	[redacted]
120 mg, twice daily	[redacted]	[redacted]
80 mg, twice daily	[redacted]	[redacted]
40 mg, twice daily	[redacted]	[redacted]

[a]A treatment cycle is 4 weeks. It is assumed that a 4-week supply of drug is dispensed to patients with no disease progression at the beginning of each 4-week period.
Abbreviations: NSCLC: non-small cell lung cancer.

Administration costs

Administration costs were based on NHS Reference Costs 2019/20[96] and PSSRU 2021.[125] For selpercatinib (an oral drug), 12 minutes of pharmacy time based on a Band 6 hourly wage (£9.60)[126] was assumed every 30 days (consistent with the assumption in NICE TA520).[124]

During treatment with any of the three interventions, patients were assumed to have one oncologist visit every 3 weeks (consistent with NICE TA520; £66,73).[124] In addition, in alignment with the SmPC, patients treated with selpercatinib received 7 ECGs.[20]

The drug administration costs used in this submission are reported in Table 59.

Table 59: Drug administration and monitoring costs for selpercatinib and comparators

Parameter	Cost (£)	Source
Administration		
Selpercatinib	9.60	PSSRU 2021;[126] NICE TA 520 (12 min pharmacy time)[124]
Pembrolizumab combination therapy	747.00	NICE TA 557;[127] NHS 2019/20[96] SB14Z + SB15Z Outpatient (30min+10min+15min IV infusion)
Pemetrexed plus platinum chemotherapy	406.00	NICE TA 557;[127] NHS 2019/20[96] SB14Z Outpatient (10min+15min IV infusion)
Monitoring		
Oncologist visit (all interventions)	125	NHS Reference costs 2019/20;[96] NICE TA520[124]
ECG (7 required for selpercatinib only)	107.00 per ECG	NHS Reference costs 2019/20[96]

Abbreviations: ECG: electrocardiogram; NHS: National Health Services; NICE: National Institute for Health and Care Excellence.

Subsequent treatments

The cost of subsequent systemic treatment was assumed to be independent of survival post-progression and was applied in the model as a one-off cost at the time of disease progression.

In the base case analysis, the distribution of subsequent treatments for NSCLC following first-line therapy was informed by NICE TA584, TA531, and TA484.[69, 71, 100] For immunotherapies, estimates in TA584 for atezolizumab combination therapy was assumed to apply to the immunotherapy comparator (pembrolizumab combination therapy). For selpercatinib, estimates were based on subsequent treatments applied to other targeted treatments in non-squamous NSCLC. The estimates for subsequent treatment distribution are presented in Table 60.

A scenario analysis was conducted in which the proportions of subsequent treatments were based of those provided by an expert oncologist consulted as part of the appraisal process. The values used for this scenario analysis are presented in Table 61.

The cost considered the time on treatment for subsequent therapy, associated administration costs, and the fraction of the patients receiving each post-progression therapy.

Table 60: Subsequent therapy distributions: base case analysis

Therapy	% Patients After Selpercatinib	% Patients After Chemotherapy/ Immunotherapy combination therapy	% Patients After Chemotherapy
Docetaxel	56.00	100.00	15.00
Nivolumab	0.00	0.00	34.00
Pembrolizumab	0.00	0.00	34.00
Atezolizumab	0.00	0.00	17.00
Pemetrexed + platinum chemotherapy	44.00	0.00	0.00

Abbreviations: NSCLC: non-small cell lung cancer.
Sources: NICE TA484;[100] NICE TA531;[69] NICE TA584.[71]

Table 61: Subsequent therapy distributions: scenario analysis (expert values)

Therapy	% Patients After Selpercatinib	% Patients After Chemotherapy	% Patients After Chemotherapy/ Immunotherapy combination therapy
Docetaxel	0	8	10
Docetaxel plus nintedanib	0	32	40
Nivolumab	0	2	2
Pembrolizumab + pemetrexed + platinum chemotherapy[a]	5	0	0
Atezolizumab / pembrolizumab	5	28	13
Pemetrexed + platinum chemotherapy	70	0	0
Best supportive care	20	30	35

Footnote: [a]Pembrolizumab plus pemetrexed plus platinum-based chemotherapy is not recommended by NICE for second-line use in advanced NSCLC patients. Due to reimbursement restrictions, the following %s are explored in a scenario analysis. After selpercatinib: 80% pemetrexed plus platinum-based chemotherapy, 20% BSC; After chemotherapy: As per table; After chemotherapy/immunotherapy combination: 15% docetaxel, 50% nintedanib plus docetaxel, 35% BSC.

B.3.4.2 Health-state unit costs and resource use

The types of resource and frequency of use in the progression-free and progressed health states included in the cost-effectiveness analysis were based on those reported in previous technology appraisal TA654 for osimertinib in EGFR mutation positive NSCLC.[98] Osimertinib represents another targeted treatment option in NSCLC and therefore resource use estimates were considered a reasonable proxy. Resource use estimates are reported per health state in Table 62. The per cycle cost for the PFS health state was £74.79, whilst the per cycle costs for PD was £118.10.

A scenario analysis was conducted in which resource use estimates were based of those provided by an expert oncologist consulted as part of the appraisal process. The values used for this scenario analysis are presented in Table 63 below.

Table 62: Resource use per 30-day period by health state: base case

Resource	Progression free	Progressed disease	Unit cost, £	Total PF, £	Total PD, £
Outpatient visit	0.79	0.65	125.00	98.75	81.25
Chest radiography	0.56	0.53	32.73	18.33	17.35
CT scan (chest)	0.05	0.02	120.55	6.03	2.41
CT scan (other)	0.03	0.03	120.55	3.62	3.62
ECG	0.09	0.07	107.00	9.63	7.49
Community nurse visit	0.71	0.71	24.55	17.43	17.43
Clinical nurse specialist	0.99	0.99	110.00	108.90	108.90

GP surgery	0.99	0.00	50.31	49.81	0.00
GP home visit	0.00	2.14	73.96	0.00	158.27
Therapist visit	0.00	2.14	48.00	0.00	102.72

Abbreviations: CT: Computerised tomography; ECG: electrocardiogram; GP: general practitioner; NSCLC: non–small cell lung cancer; PD: progressed disease; PF: progression free.
Source: TA654,[98] NHS Reference Costs 2019–20,[96] PSSRU 2019.[128]

Table 63: Resource use per year, by health state: scenario analysis (expert values)

Resource	Frequency per year	
	Progression-Free	Progressed
Outpatient visit	12–13	12–13
Chest radiography	7	6
CT scan (chest and upper abdomen)	4	4
CT scan (other)	0.8	0.4
Brain MRI	1	(Not provided)
ECG	6	1
Community nurse visit	2–3	2–3
Clinical nurse specialist	12	12
GP surgery	12	0
GP home visit	2	4–6
Therapist visit	0	(Not provided)

Abbreviations: CT: Computerised tomography; ECG: electrocardiogram; GP: General practioner; MRI: magnetic resonance imaging.
Source: Eli Lilly and Company Ltd. Data on file. Clinical Validation Meeting Minutes.[17]

B.3.4.3 Adverse reaction unit costs and resource use

Mean cost per adverse event applied in the cost-effectiveness analyses are reported in Table 64. Adverse event costs were applied in the model according to the incidences presented in Section B.3.3.4.

Table 64: Costs per adverse event applied in the cost-effectiveness model

Adverse event	Mean cost, £	Source
Diarrhoea	4,443.85	NHS Reference costs 2019/20; TA621
Hypertension	967.40	NHS Reference costs 2019/20; TA516
ECG QT prolonged	902.89	NHS Reference costs 2019/20; TA516
Abdominal pain	0.00	NHS Reference costs 2019/20; Assumption
Haemorrhage	0.00	Assumption
Fatigue	2,886.14	NHS Reference costs 2019/20; TA621
Decreased appetite	0.00	NHS Reference costs 2019/20; TA516
Rash	0.00	NHS Reference costs 2019/20; TA621
Asthenia	2,886.14	NHS Reference costs 2019/20; TA621
Vomiting	4,443.85	NHS Reference costs 2019/20; Assumption
Dyspnoea	0.00	NHS Reference costs 2019/20; TA484

Alanine aminotransferase increased	4,231.62	NHS Reference costs 2019/20; TA621
Aspartate aminotransferase increased	4,231.62	NHS Reference costs 2019/20; TA621
Hyponatraemia	0.00	Assumption
Lymphopenia	4,517.24	NHS Reference costs 2019/20; Assumption
Pneumonia	2,465.50	NHS Reference costs 2019/20; Assumption
Dehydration	0.00	Assumption
Thrombocytopenia	3,100.40	NHS Reference costs 2019/20; Assumption
Neutropenia	3,181.31	NHS Reference costs 2019/20; Assumption
Anaemia	1,363.57	NHS Reference costs 2019/20; TA520
Pleural effusion	3,165.18	NHS Reference costs 2019/20; Assumption
Febrile neutropenia	5,848.60	TA484
Pyrexia	0.00	Assumption
Pneumonitis	3,997.83	NHS Reference costs 2019/20; Assumption
Nausea	4,443.85	NHS Reference costs 2019/20; Assumption
Hepatitis Lab abnormalities	2,886.14	Assumption
Hypothyroidism	4,443.85	Assumption
Hyperthyroidism	0.00	Assumption
Cellulitis	4,231.62	Assumption
Sepsis	4,231.62	NHS Reference costs 2019/20; Assumption

Abbreviations: ECG: echocardiogram; NHS: National Health Service; SE: standard error; TA: technology appraisal.
Source: NHS Reference Costs 2019/120;[96] TA654;[98] TA516;[129] TA484;[100] TA520.[124]

B.3.4.4 Miscellaneous unit costs and resource use

A one-off end of life cost of £4,189.76 (Table 65) was also included based on costs included in TA654,[98] which considered hospital admission and excess bed days, Macmillan nurse home visits and hospice care stays.

Table 65: End of life costs in the second line setting

	Mean	Patients, proportion	Unit costs, £	Total cost, £
Hospital admission	1.00	55.8%	4,293.60	2,395.83
+ excess bed days	0.92	55.8%	1,710.27	877.98
Macmillan nurse home visits	1.00	27.3%	32.67	8.92
Hospice care stay	1.00	16.9%	5,367.01	907.02

Source: TA654[98]

As described in Section B.1.3, due to the imminent establishment of Genomic Hubs, whereby testing for RET and other genetic mutations of tumour samples will become routine, it is believed that no costs for genetic testing should be included in the analysis. However, a proportional cost

of [redacted] per tested patient provided by NHSE&I for the appraisal of selpercatinib in pre-treated advanced RET-fusion NSCLC (TA760) was applied in the base case.

B.3.5 Severity

The severity modifier tool developed by ScHAAR and Lumanity was used to calculate the absolute and proportional severity modifiers.[130] A summary of the features of the QALY shortfall analysis is provided in Table 66. In line with the NICE reference case,[95] the Hernandez-Alava 2017 study,[131] which mapped the EQ-5D-5L to the 3L, was used to inform the base case economic analysis. However, a number of sources were explored in scenarios, as presented in Table 67, all of which led to a QALY modifier of 1.2, and a corresponding WTP threshold of £36,000 per QALY. This WTP threshold was therefore considered for the base case economic analysis.

Table 66: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Sex distribution (Female)	62.3%	Section B.3.2.1
Starting age	[redacted]	Section B.3.2.1
Health state: PF	[redacted]	Section B.3.3.2
Health state: PD	[redacted]	Section B.3.3.2

Abbreviations: PD: progressed disease; PF: progression free; QALY: quality adjusted life year.
Source: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[80]

Table 67: Summary of QALY shortfall analysis

HRQoL norms source	Expected remaining QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
Base case: Hernandez Alava et al., EQ-5D-5L mapped to 3L plus HSE 2017–2018	[redacted]	Pembrolizumab combination: [redacted]	10.28	87.05%	**X1.2**
Base case: Hernandez Alava et al., EQ-5D-5L mapped to 3L plus HSE 2017–2018	[redacted]	Pemetrexed plus platinum based chemotherapy: [redacted]	10.81	91.53%	**X1.2**
Van Hout et al., EQ-5D-5L mapped to 3L plus HSE 2017–2018	[redacted]	Pembrolizumab combination: [redacted]	10.36	87.13%	**X1.2**
Van Hout et al., EQ-5D-5L mapped to 3L plus HSE 2017–2018	[redacted]	Pemetrexed plus platinum based chemotherapy: [redacted]	10.89	91.59%	**X1.2**
VH EQ-5D-3L value set plus health state profiles	[redacted]	Pembrolizumab combination: [redacted]	10.26	87.03%	**X1.2**
MVH EQ-5D-3L value set plus health state profiles	[redacted]	Pemetrexed plus platinum based chemotherapy: [redacted]	10.79	91.52%	**X1.2**
MVH EQ-5D-3L value set + HSE 2012–2014	[redacted]	Pembrolizumab combination: [redacted]	10.59	87.38%	**X1.2**
MVH EQ-5D-3L value set + HSE 2012–2014	[redacted]	Pemetrexed plus platinum based chemotherapy: [redacted]	11.12	91.75%	**X1.2**

Abbreviations: EQ-5D-3/5L: Euro-QoL Questionnaire 5 Dimensions 3/5 levels; HSE: Health Survey for England; MVH: Measurement and Valuation of Health study; QALY: quality-adjusted life year.

B.3.6 Uncertainty

RET-fusion positive advanced NSCLC is a rare condition, occurring in approximately 1–2% of NSCLC cases (Section B.1.3.1).[2] As such, in order to generate relative efficacy estimates for selpercatinib compared to relevant comparators, data from advanced NSCLC studies where *RET* fusion-positive patients were not specifically recruited for, nor their status tested or reported, had to be included in the NMA. Whilst this may be considered to potentially result in uncertainty in the relative efficacy estimates, studies such as Hess *et al.* have confirmed that the real prognostic influence of *RET* mutations remains unclear (see Section B.1.3.1) and therefore, as specified in Section B.2.8, adjustments relating to the presence of *RET* fusion were not made to these data.[31] This assumption is in line with the accepted assumption in TA760 for selpercatinib in the pre-treated setting.[12]

Furthermore, the data for OS from LIBRETTO-001 is currently immature, which may lend some uncertainty to the analysis. This was mitigated through detailed consultations with UK-based expert oncologists regarding anticipated long-term survival for *RET* fusion-positive NSCLC treated with selpercatinib, to generate as clinically valid long-term extrapolations as possible.[17] In addition, as described further in Section B.3.7, future data cuts of LIBRETTO-001 will produce more mature data, and further OS data for selpercatinib will be collected in an ongoing Phase III study (LIBRETTO-431).

B.3.7 Managed access proposal

Selpercatinib may be a candidate for a recommendation through the CDF. As demonstrated by the results presented in B.3.9, selpercatinib has the potential to represent a cost-effective use of resource versus relevant comparators. However, Eli Lilly acknowledge uncertainty may remain in the cost-effectiveness analysis due to immature OS data for selpercatinib from LIBRETTO-001. However, plans to collect further OS to inform the analysis are in place, specifically:

- Future data cuts of LIBRETTO-001; next datacut in [redacted] but may be available after the timeframe of this appraisal
- Results from the LIBRETTO-431 trial, a Phase III study of treatment-naïve patients for metastatic *RET* fusion-positive NSCLC, which is planned to enrol ~250 participants.[14] The study includes pemetrexed and platinum chemotherapy, with or without pembrolizumab, which is directly relevant to the decision problem of this evaluation. The primary outcome is PFS by blinded independent committee review (BICR). Secondary outcomes include ORR, DOR and OS. Interim results for LIBRETTO-431 are expected in December 2023.[14]

Should selpercatinib receive a recommendation through the CDF, these two sources would be used to inform the evidence base for the cost-effectiveness analysis in the re-submission to NICE.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of inputs for the base case analysis is presented in Table 68.

Table 68: Summary of variables applied in the economic model (base case analysis)

Variable	*RET*-fusion positive NSCLC	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings			
Discount rate (costs)	3.5%	-	Section B.3.10.3
Discount rate (benefits)	3.5%	-	
Time horizon	Lifetime: 25 years	N/A	
Patient characteristics			
Median age	[redacted]	Normal	Section B.2.3.4
Percent female	62.3%	Beta	
Median weight	[redacted]	Normal	
Clinical inputs			
OS (selpercatinib)	Spline knot 1	N/A	Section B.3.2
PFS (selpercatinib)	Gompertz	N/A	
OS (reference arm and comparators)	Spline knot 1	N/A	
PFS (reference arm and comparators)	Gompertz	N/A	
NMA HRs (comparators)	*Various*	N/A	Section B.2.8.3
TTD (selpercatinib)	Exponential	N/A	Section B.3.2.4
Adverse events, incidence	*Various*	N/A	Section B.3.2.5
Utility inputs			
Utility for PF	[redacted]	Beta	Section B.3.3
Utility for PD	[redacted]	Beta	
Drug acquisition costs			
Selpercatinib price: 60 x 80 mg tablets	[redacted]	N/A	Section B.3.4.1
Selpercatinib price: 60 x 40 mg tablets	[redacted]	N/A	
Pembrolizumab: 4 ml (25 mg/ml vials)	£2,630.00	N/A	
Pemetrexed price: 1 x 100 mg powder	£128.00	N/A	

Carboplatin: 45 ml (10mg/ml vials)	£6.08	N/A	
Include drug wastage	Yes	N/A	Section B.3.4.1
Cost per treatment cycle: selpercatinib	*Various*	N/A	Section B.3.4.1
Cost per treatment cycle: comparators	*Various*	N/A	
Drug administration costs			
Selpercatinib	£9.60	Gamma	Section B.3.4.1
Pembrolizumab combination	£747.00	Gamma	
Pemetrexed + platinum chemotherapy	£406.00	Gamma	
Monitoring costs			
Oncologist visit	£125.00	Gamma	
ECG (selpercatinib specific)	£107.00 per ECG	Gamma	
Subsequent therapy			
Selpercatinib	£1,426.95	Beta	Section B.3.4.1
Immunotherapy	£1,418.81	Beta	
Chemotherapy	£18,129.57	Beta	
Health state costs			
Health state costs per cycle: PFS	£74.79	Beta	Section B.3.4.2
Health state costs per cycle: PD	£118.10	Beta	
Other costs			
Adverse event costs	*Various*	Gamma	Section B.3.4.4
End of life costs	£4,189.76	Gamma	Section B.3.4.4

Footnote: SEs varied in the PSA are reported where applicable.
Abbreviations: HR: hazard ratio; NA: not applicable; NMA: network meta-analysis; OS: overall survival; PD: progressed disease; PFS: progression free survival; PPS: post progression survival; PSA: probabilistic sensitivity analysis; SE: standard error.

B.3.8.2 Assumptions

A list of the key assumptions used in the base case analysis is provided in Table 69.

Table 69: Modelling assumptions

Parameter (setting)	Assumption	Justification	Addressed in scenario analysis
PFS and OS comparator arm extrapolations	The parametric survival function selected for the reference arm was deemed appropriate to represent PFS and OS for pembrolizumab combination therapy.	This assumption was necessary in order to generate OS and PFS extrapolations for comparators to selpercatinib relevant to the decision problem through application of HRs from the NMAs.	Alternative parametric survival functions for PFS and OS for all comparators are explored in scenario analyses.
Patients baseline *RET* status	Treatment effect estimates for the comparator interventions observed in trials predominantly enrolling patients with wild-type tumours are generalisable to patients with *RET*-fusion tumours.	This assumption was necessary due to comparator RCTs not testing patients for *RET* fusion at enrolment, and is supported by an analysis of 5,807 NSCLC patients (*RET* positive: 46; *RET* negative: 5,761), which found that after adjusting for baseline covariates, no statistically significant prognostic effect of *RET* fusion status on PFS or OS existed.[31]	N/A
Proportional hazards assumption	The NMAs informing the economic analysis assumed proportional hazards, although there was evidence for some trials informing the NMA that the proportional hazards assumption was violated.	This was considered an acceptable limitation given the degree of overall uncertainty in the indirect comparison and limited OS data available for selpercatinib.	Alternative parametric survival functions for PFS and OS in both settings are explored in scenario analyses, including applying treatment specific curves.
Adverse events	Adverse events are assumed to occur in the first cycle of the model only.	This approach is in line with previous appraisals in NSCLC.[12, 18]	N/A
Dose reductions	A weighted mean dosage was applied to the costs of selpercatinib based on dosage data collected in LIBRETTO-001. In the absence of dose reduction data for the	To account for anticipated dose reductions with each therapy.	N/A

	comparators, the equivalent relative dose intensity as selpercatinib was assumed for pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy.		
Administration costs	For selpercatinib and other oral drugs, 12 minutes of Band 6 pharmacy time (£9.60)[126] was assumed every 30 days.	Consistent with the assumption in prior NICE appraisal TA520.[124]	N/A
Subsequent treatments	The cost of subsequent systemic treatment was assumed to be independent of survival post-progression and was applied in the model as a one-off cost at the time of disease progression.	This assumption was made for simplicity taking into account the partitioned survival structure of the model, which does split survival by post-progression therapy.	N/A
	The pattern of subsequent treatments was informed by previous appraisals for comparable therapies, i.e. targeted therapies for selpercatinib, and immunotherapies for pembrolizumab combination therapy.	This approach was validated by UK expert clinicians.[17]	Alternative subsequent treatment patterns selected by an expert oncologist consulted as part of the appraisal process are explored in a scenario analysis.[17]

Abbreviations: CrI: credible interval; HR: hazard ratio; HRQoL: health-related quality of life; HSUVs: health state utility values; IV: intravenous; NMA: network meta-analysis; NGS: next generation sequencing; NSCLC: non-small cell lung cancer; OS: overall survival;; PFS: progression free survival; RDI: relative dose intensity.

B.3.9 Base-case results

B.3.9.1 Base-case incremental cost-effectiveness analysis results

The base case deterministic and probabilistic cost-effectiveness results for selpercatinib versus pembrolizumab combination therapy and pemetrexed plus platinum-based chemotherapy are presented in Table 70 and Table 71, respectively. In the deterministic analyses selpercatinib was found to be cost-effective compared to all relevant comparators at a willingness to pay (WTP) threshold of £36,000 per QALY, yielding an ICER of £5,264 and £35,883 when compared to pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy, respectively.

The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix J.

The base case deterministic and probabilistic fully incremental results for selpercatinib versus pembrolizumab combination therapy and pemetrexed plus platinum-based chemotherapy are presented in Table 70 and Table 71, respectively

Table 70: Deterministic base-case results (with PAS)

Intervention	LYs	QALYs	Costs (£)	Incremental LYs	Incremental QALYs	Incremental Costs	Pairwise ICER (selpercatinib vs comparator) (£/QALY)	NHB	Fully Incremental ICER (£/QALY)
Pemetrexed + platinum chemotherapy	1.298	[redacted]	[redacted]	3.367	[redacted]	[redacted]	35,883	[redacted]	N/A
Pembrolizumab + pemetrexed + platinum chemotherapy	1.972	[redacted]	[redacted]	2.693	[redacted]	[redacted]	5,264	[redacted]	Extendedly dominated
Selpercatinib	4.665	[redacted]	[redacted]	-	[redacted]	[redacted]	-	-	35,883

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; NSCLC: non-small cell lung cancer; QALYs: quality-adjusted life years.

Table 71: Probabilistic base-case results (with PAS)

Intervention	LYs	QALYs	Costs (£)	Incremental LYs	Incremental QALYs	Incremental Costs	Pairwise ICER (selpercatinib vs comparator) (£/QALY)	Fully Incremental ICER (£/QALY)
Pemetrexed + platinum chemotherapy	1.323	[redacted]	[redacted]	3.353	[redacted]	[redacted]	36,025	N/A
Pembrolizumab + pemetrexed + platinum chemotherapy	2.001	[redacted]	[redacted]	2.673	[redacted]	[redacted]	5,209	Extendedly dominated
Selpercatinib	4.676	[redacted]	[redacted]	-	[redacted]	[redacted]	-	36,078

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; NSCLC: non-small cell lung cancer; QALYs: quality-adjusted life years.

B.3.10 Exploring uncertainty

Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses the results of which are presented in Sections B.3.10.1 and B.3.10.2, respectively. In addition, key assumptions in the model were explored in several probabilistic scenario analyses, the results of which are presented in Section B.3.10.3. Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

B.3.10.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were run with 1,000 iterations, with estimates of model parameters based on the uncertainty in the source data (where data availability permitted). Where no such data were available, the model applied a user-defined percentage of the mean value as the standard error. An ICER convergence plot is provided in Figure 28 below.

Figure 28: ICER convergence plot

Abbreviations: ICER: incremental cost-effectiveness ratio.

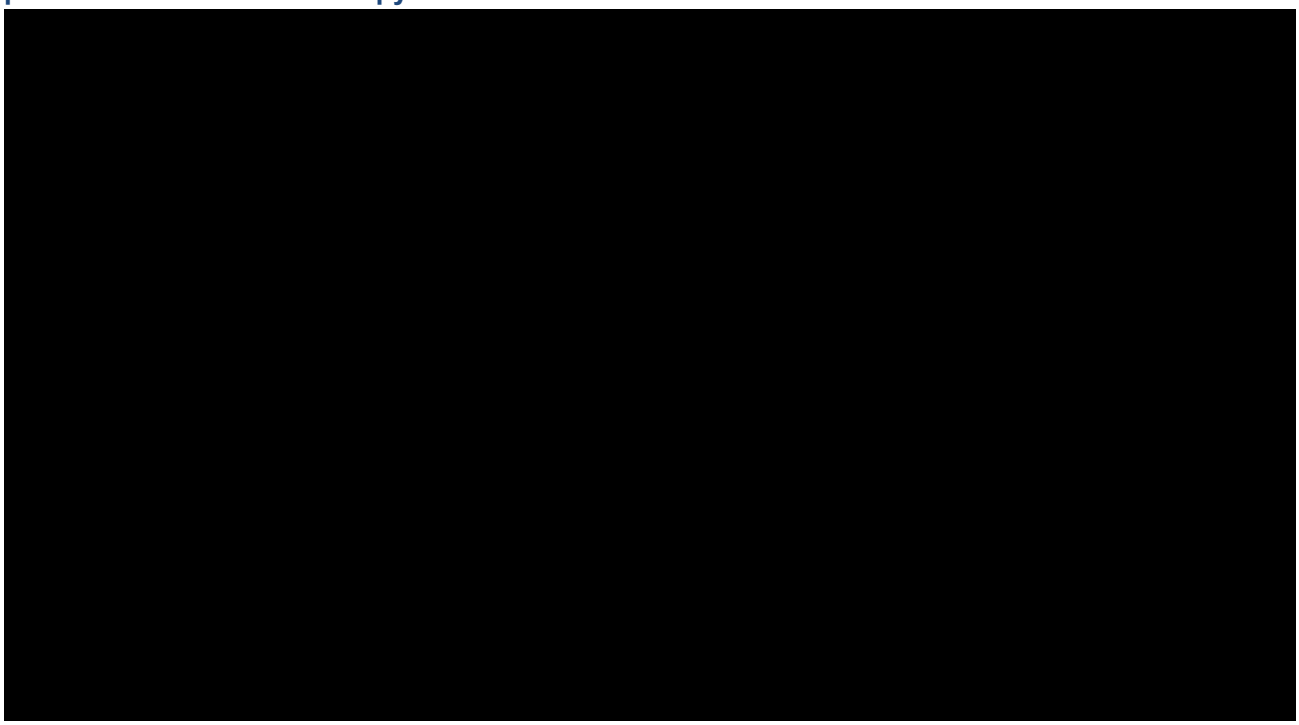
The probabilistic cost-effectiveness planes for selpercatinib versus pembrolizumab combination therapy and pemetrexed plus platinum based chemotherapy are presented in Figure 29 and Figure 30, respectively.

The cost-effectiveness acceptability curves for selpercatinib versus pembrolizumab combination therapy and pemetrexed plus platinum based chemotherapy is presented in Figure 31. The PSA found the probability of selpercatinib being cost-effective to be [redacted] and [redacted] at a WTP threshold of £30,000 and £40,000 per QALY, respectively.

Figure 29: Probabilistic cost-effectiveness plane for selpercatinib vs pembrolizumab combination therapy

Abbreviations: QALY: quality-adjusted life year.

Figure 30: Probabilistic cost-effectiveness plane for selpercatinib vs pemetrexed plus platinum based chemotherapy



Abbreviations: QALY: quality-adjusted life year.

Figure 31: Cost-effectiveness acceptability curve for selpercatinib vs pembrolizumab combination therapy and pemetrexed plus platinum based chemotherapy

Abbreviations: QALY: quality-adjusted life year.

B.3.10.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, deterministic sensitivity analyses (DSA) were conducted. The tornado diagrams for selpercatinib versus pembrolizumab combination therapy and pemetrexed plus platinum-based chemotherapy are presented in Figure 32 and Figure 33, respectively. The top 25 most influential parameters on the base case are presented in each case.

A small number of inputs had a significant impact on the ICER when varied to their limits across all pairwise comparisons and both treatment lines. For pembrolizumab combination therapy, the inputs that had the greatest impact on the ICER were discount rate costs, drug administration costs and discount rate outcomes. For pemetrexed plus platinum-based chemotherapy, the inputs that had the greatest impact on the ICER were discount rate outcomes, discount rate costs and adverse event costs (progressed disease). Discount rate for costs and effects used in the model aligned with NICE reference case (3.5%).

Figure 32: DSA tornado diagram for selpercatinib vs pembrolizumab combination therapy

Abbreviations: DSA: deterministic sensitivity analysis; ECG: electrocardiogram.

Figure 33: DSA tornado diagram for selpercatinib vs pemetrexed plus platinum-based chemotherapy

Abbreviations: DSA: deterministic sensitivity analysis; ECG: electrocardiogram.

B.3.10.3 Scenario analysis

Several scenario analyses were conducted to assess the impact of the uncertainty associated with key inputs and assumptions in the economic model. A summary of the scenario analysis results for selpercatinib versus relevant comparators are presented in Table 72. It should be highlighted that for scenario analyses on the OS and PFS curves, unless otherwise noted, the specified parametric function was applied to both selpercatinib and the reference arm.

Owing to the uncertainty surrounding the survival curve choice, scenario analyses investigating key alternative survival curve options for PFS, OS and TTD were run both probabilistically and deterministically. Due to the computational burden and long run time of the probabilistic sensitivity analyses, all other scenarios were run deterministically. The probabilistic results of the survival curve scenario analyses were closely aligned with the deterministic results providing confidence in the deterministic results for the remaining scenario analyses.

The results of the scenario analyses demonstrated that the base case ICERs were most sensitive to variations in the survival functions used to extrapolate OS and the distribution of subsequent therapies. However, none of the scenario analyses resulted in a substantial change to the base case ICERs.

Table 72: Scenario analysis results for selpercatinib versus relevant comparators

Scenario		Selpercatinib vs pembrolizumab + pemetrexed + platinum chemotherapy			Selpercatinib vs pemetrexed + platinum chemotherapy		
		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	***5,294***	[redacted]	[redacted]	***35,883***
1	Discount rate: Benefits & Costs 1.5%	[redacted]	[redacted]	7,258	[redacted]	[redacted]	34,855
2	Utilities: TA654	[redacted]	[redacted]	5,539	[redacted]	[redacted]	37,603
3	Curve choice PFS: Exponential	[redacted]	[redacted]	3,995	[redacted]	[redacted]	35,587
	Probabilisitic results	[redacted]	[redacted]	3,759	[redacted]	[redacted]	35,166
4	Curve choice PFS: Weibull	[redacted]	[redacted]	7,974	[redacted]	[redacted]	36,105
	Probabilisitic results	[redacted]	[redacted]	7,907	[redacted]	[redacted]	36,352
5	Curve choice PFS: Stratified Weibull	[redacted]	[redacted]	8,084	[redacted]	[redacted]	36,098
6	Curve choice PFS: Spline knot 1	[redacted]	[redacted]	4,296	[redacted]	[redacted]	35,430
7	Separate comparator curve choice OS: Spline knot 3	[redacted]	[redacted]	5,413	[redacted]	[redacted]	35,361
8	Curve choice OS: Spline knot 3	[redacted]	[redacted]	4,923	[redacted]	[redacted]	39,466
9	Separate comparator curve choice OS: Exponential	[redacted]	[redacted]	4,953	[redacted]	[redacted]	36,888

	Probabilisitic results	[redacted]	[redacted]	5,154	[redacted]	[redacted]	36,038
10	Curve choice OS: Exponential	[redacted]	[redacted]	5,412	[redacted]	[redacted]	33,563
	Probabilisitic results	[redacted]	[redacted]	5,359	[redacted]	[redacted]	33,513
14	Curve choice TTD: Gompertz	[redacted]	[redacted]	-2,026	[redacted]	[redacted]	30,068
	Probabilisitic results	[redacted]	[redacted]	-2,130	[redacted]	[redacted]	29,771
15	Curve choice TTD: Weibull	[redacted]	[redacted]	3,273	[redacted]	[redacted]	34,295
16	Curve choice TTD: gamma	[redacted]	[redacted]	4,267	[redacted]	[redacted]	35,088
17	Expert subsequent therapy distribution	[redacted]	[redacted]	5,194	[redacted]	[redacted]	39,542
18	Expert HCRU estimates	[redacted]	[redacted]	4,719	[redacted]	[redacted]	35,547

Abbreviations: HCRU: healthcare resource use; ICER: incremental cost-effectiveness ratio; N/A: not applicable; OS: overall survival; PFS: progression-free survival; TTD: time-to-treatment discontinuation.

B.3.11 Subgroup analysis

N/A - no subgroups were considered relevant to this appraisal and as such no subgroup analyses were included in the cost-effectiveness analysis.

B.3.12 Benefits not captured in the QALY calculation

If recommended, selpercatinib will be the first RET receptor kinase inhibitor to become available for treatment-naïve *RET*-fusion positive advanced NSCLC patients in the UK. Currently, these patients receive the same treatments as those without recognised oncogenic markers. Prognosis in these patients is poor; people diagnosed with advanced NSCLC have a significantly reduced chance of survival: around 57% of people diagnosed at the early stages of disease will survive for five years or longer, whilst only 3% of those diagnosed with advanced disease will survive as long.[4] On top of physical disease symptoms, people with this condition experience anxiety and depression due to the impact of diagnosis, conversation around the disease, impact of treatment and predicted course of the disease.[53] The availability of a novel treatment that is specifically targeted to the oncogenic driver of their condition may offer hope to patients and their families of delayed disease progression and improved survival. This is not captured in the QALY calculations.

In addition, owing to its targeted mechanism of action, selpercatinib is associated with a tolerable safety profile, unlike current clinical management, which is often associated with off-target side effects. A recent survey conducted by Young *et al.* (2021) investigating preferences for first-line treatments of advanced NSCLC in 308 treatment-naive patients and 188 caregivers, found patients valued treatments which were not associated with AEs that may lead to hospitalisation.[132] This patient preference for a treatment with an improved safety profile is not captured in the QALY calculations.

A final notable benefit of selpercatinib is that it has a convenient oral method of administration. Current alternatives to selpercatinib in UK clinical practice require intravenous infusion, and therefore need to be administered in a specialised infusion clinic, resulting in a greater economic burden on NHS resources. In addition, a review of the scientific literature reporting on patient preferences (including lung cancer patients) for oral compared to IV administration of cancer treatments by Eek *et al*. (2016) found the majority (84.6%) of studies reported that patients preferred oral administration.[133] Oral treatments were preferred owing to their increased ease of administration and ability to self-administer from home, reducing the need to travel to infusion clinics.[133] Further to this, the survey conducted by Young *et al.* (2021), described above, found caregivers prefer treatments that are quick to administer.[132] These patient and caregiver preferences for a novel treatment with a convenient oral method of administration that is quick to administer are not captured in the QALY calculations.

B.3.13 Validation

Face validity

Model validations were performed in alignment with best practices.[134] The model structure, source data and statistical analysis design were reviewed by external experts, including a health economist and UK clinical experts in NSCLC.[17] Of note, and as discussed in Section B.3.13, in light of the currently immature OS data available from the LIBRETTO-001 trial, a thorough clinical

validation process was conducted in order to inform survival analysis for the OS extrapolations selected for the base case analysis.

Internal validity

Quality-control procedures for verification of input data and coding were performed by health economists not involved in the model development and in accordance with a pre-specified test plan. These procedures included verification of all input data with original sources and programming validation. Verification of all input data was documented (with the initials of the health economist performing the quality-control procedure and the date the quality-control procedure was performed) in the relevant worksheets of the model. Any discrepancies were discussed, and the model input data was updated where required. Programming validation included checks of the model results, calculations, data references, model interface, and Visual Basic for Applications code.

External validity

Due to the median PFS and OS not yet having been reached in the LIBRETTO-001 trial for the SAS1 population it was not possible to conduct external validation of model outcomes for selpercatinib against trial data. However, clinical feedback was used to validate the curve choices used to extrapolate the trial data over the lifetime time horizon of the model (see Section B.3.2).[17] In addition, model estimates for median PFS and OS for selpercatinib were consistent with real-world data obtained by Tan *et al.* (2020) in *RET*-fusion positive NSCLC patients receiving selective TKI in clinical practice (**Error! Reference source not found.**).[52] Model estimates for median PFS and OS for both pembrolizumab combination therapy and pemetrexed plus platinum based chemotherapy were also found to be consistent with estimates obtained during the Phase III KEYNOTE trial in untreated, metastatic non-squamous NSCLC patients, suggesting the survival extrapolations were associated with high external validity.[109]

Clinical feedback was also used to validate the resource use inputs utilised in the model, including subsequent treatment choices and monitoring frequencies. Where possible, UK source were used for model inputs and similar inputs and approaches to those used in prior appraisal were adopted.[17]

Table 73: External validation of model outcomes against published PFS and OS estimates (months)

	Trial mPFS	Predicted mPFS	Trial mOS	Predicted mOS
Selpercatinib	21.95 (LIBRETTO-001)	[redacted]	49.3 (Tan *et al.* 2020)[52]	[redacted]
Pembrolizumab + pemetrexed + platinum chemotherapy	9.0 (KEYNOTE)-189)[109]	[redacted]	22.0 (KEYNOTE)-189)[109]	[redacted]
Pemetrexed + platinum chemotherapy	4.9 (KEYNOTE)-189)[109]	[redacted]	10.6 (KEYNOTE)-189)[109]	[redacted]

Abbreviations: ITT: intent-to-treat; mOS: median overall survival; mPFS: median progression free survival.
Sources: Tan *et al.* (2020). KEYNOTE-189.[52, 109] Drilon *et al.* 2022.[78]

B.3.14 Interpretation and conclusions of economic evidence

Summary of the cost-effectiveness evidence

In order to assess the cost-effectiveness of selpercatinib versus relevant comparators in patients with *RET*-fusion positive advanced NSCLC in the UK, a *de novo* cost-effectiveness analysis was conducted from the perspective of the NHS and PSS in England. *RET* fusion-positive NSCLC was associated with a severity modifier of 1.2 on the QALY, thus leading to a willingness-to-pay threshold of £36,000 per QALY.

In the deterministic base case analysis selpercatinib was found to be cost-effective compared to both comparators at a WTP of £36,000 per QALY and thus selpercatinib can be considered a cost-effective use of NHS resources in treatment-naïve patients with *RET*-fusion positive advanced NSCLC. The ICER for selpercatinib versus pembrolizumab combination therapy and pemetrexed plus platinum-based chemotherapy was £5,264 and £35,883, respectively.

The PSA found the probability of selpercatinib being cost-effective to be [redacted] and [redacted] at a WTP threshold of £30,000 and £40,000 per QALY, respectively. The DSA results identified a small number of key influential parameters including the discount rate applied to costs and outcomes, the adverse event costs associated with progressed disease and the drug administration costs for pembrolizumab combination therapy, however, overall the model was largely robust to uncertainty in the majority of parameters. Scenario analyses conducted to address sources of uncertainty in the model demonstrated that whilst there was variation in the ICER, the cost-effectiveness conclusions remained largely the same, with selpercatinib remaining cost-effective at a WTP of £36,000 per QALY across the majority of scenarios.

Strengths

A robust clinical validation exercise was conducted by Eli Lilly with two expert oncologist practising in the UK in order to validate key inputs and assumptions, including survival extrapolations for OS, PFS and TTD, HCRU and subsequent treatments.[17] Validation of survival extrapolations was particularly important given that no long-term survival data is currently available for *RET* fusion positive NSCLC patients. In addition, the clinical experts reviewed the baseline characteristics of patients enrolled in the LIBRETTO-001 trial and the comparator choice both of which were subsequently deemed to be representative of UK clinical practice. The results of the economic analysis are therefore considered highly relevant to decision-making on the introduction of selpercatinib into NHS clinical practice.

The cost-effectiveness analysis is associated with several strengths, the first being that many new therapies for NSCLC and those targeting genetic alterations, have been appraised by NICE. A review of relevant NICE evaluations was conducted during model design and development, and thus it was possible to take into account a number of learnings from previously developed models for NSCLC, in addition to prior external assessment group (EAG) and Committee preferences for methodological approaches in this area, such as cost and resource use and the selection of HSUVs. In particular, key learnings were taken from a recent appraisal of another *RET* fusion inhibitor in the same indication and the committee papers were reviewed to ensure, where possible, this evaluation was conducted in alignment with previous committee preferences in this area.[18]

The model further closely aligns to the NICE reference case, adopting an NHS and PSS perspective as well as utilising a lifetime time horizon to ensure all costs and QALY gains

associated with the interventions are fully capture and discounting costs and benefits at a rate of 3.5% per anum.[99]

Limitations

The key limitations of the analysis include the single-arm nature of the LIBRETTO-001 trial and the immaturity of the survival data currently available from the trial.

As discussed in Sections B.2.8 and B.3.2, in order to connect the selpercatinib arm to the NMA and produce relative efficacy versus both comparators relevant to the decision problem, it was necessary to generate a pseudo-control arm using IPD for the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial.[135] This pseudo-control arm was subsequently used as a reference in the survival analysis for the cost-effectiveness model to generate PFS and OS extrapolations for pembrolizumab combination therapy. To minimise uncertainty in this process, the pseudo-control arm was adjusted for prognostic factors through use of propensity score matching, thus accounting for key differences in characteristics between the LIBRETTO-001 and KEYNOTE-189 trial populations, and generating a reliable treatment effect estimate for the two treatments.

A further potential limitation of the relative efficacy estimates is that efficacy data for both relevant comparators was derived from trials conducted in patient populations in whom *RET* fusion was not specifically tested for/reported. However, as described in Section B.1.3.1, an analysis of 5,807 NSCLC patients (*RET* positive: 46; *RET* negative: 5,761), found that after adjusting for baseline covariates, no statistically significant prognostic effect of *RET* fusion status on PFS or OS was identified.[31] This evidence supports the approach undertaken for the indirect comparison whereby known prognostic factors have been adjusted for, thus minimising uncertainty in the analysis.

With regards to the immaturity of the OS data from LIBRETTO-001, the trial is ongoing, with upcoming data cuts anticipated to provide more mature data. In addition, Eli Lilly and Company is conducting a Phase III study (LIBRETTO-431) in treatment-naïve patients for metastatic *RET* fusion-positive NSCLC, which is planned to enroll ~250 participants.[14] The primary endpoint is PFS by IRC and the study includes a comparator arm of pemetrexed and platinum chemotherapy, with or without pembrolizumab, which is directly relevant to the decision problem for this evaluation. It is therefore planned for comparative clinical effectiveness and safety data for selpercatinib to become available, which is of importance should selpercatinib be recommended for use under the CDF. Should selpercatinib be recommended under the CDF, it is anticipated that mature OS data would be available prior to evaluation for exit.

Conclusion

There remains a considerably high unmet need amongst adult patients with untreated *RET*-fusion positive advanced NSCLC for a safe, targeted treatment option with a convenient method of administration. Selpercatinib has demonstrated superior efficacy to relevant comparators in UK clinical practice (Section B.2.8) which, as demonstrated in the LIBRETTO-001 trial, is associated with improved patient HRQoL. Selpercatinib, with its targeted mechanism of action, oral method of administration and tolerable safety profile could therefore offer a much-needed treatment option for these patients. Overall, the base case ICERs for all comparisons demonstrated selpercatinib to be cost-effective at a WTP £36,000 per QALY and thus selpercatinib can be considered a cost-effective use of NHS resources.

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Appendices

Appendix A: Summary of product characteristics (SmPC) and European public assessment report (EPAR)
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Selpercatinib for untreated *RET* fusion-positive advanced non-small cell lung cancer [ID4056]

Summary of Information for Patients

16th September 2022

File name	Version	Contains confidential information	Date
ID4056_Selpercatinib_Untreated RET NSCLC_SIP_FINAL	V1.0	No	16th September 2022

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Name of the medicine (generic and brand name):

Generic name: **Selpercatinib**
Brand name: **Retsevmo®**

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

People with advanced *RET* fusion-positive non-small cell lung cancer (NSCLC) who have not received previous treatment (untreated).

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.

Selpercatinib currently holds a conditional marketing authorisation as a stand-alone therapy for the treatment of patients with advanced *RET* fusion-positive NSCLC who require systemic treatment *following prior treatment with immunotherapy and/or platinum-based chemotherapy*, which was granted by the European Medicines Agency (EMA) on the 11th February 2021.[1] The approval can be accessed via the following link: https://www.ema.europa.eu/en/medicines/human/EPAR/retsevmo#authorisation-details-section.

A marketing authorisation application has since been submitted by Eli Lilly and Company to the UK Medicine and Healthcare Products Regulatory Agency (MHRA) for the use of selpercatinib in patients with untreated advanced *RET* fusion-positive NSCLC. This is the indication under

consideration for this NICE evaluation. Information relating to the proposed timelines for this application are provided in Document B Section B.2.1.

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:

Financial payments have been made by Eli Lilly and Company to the following organisations:

- Roy Castle Lung Cancer Foundation Global Lung Cancer Coalition – Financial contributions made in 2022, 2021 and 2019.
- United Kingdom Lung Cancer Coalition Corporate Membership – Financial contribution made in 2021
- Mesothelioma UK Stand Sponsorship – Financial contribution made in 2019

SECTION 2: Current landscape

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

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

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.
Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Main condition that the medicine plans to treat

Selpercatinib is planned to treat adult patients with *RET* fusion-positive NSCLC who have received no prior treatment since their diagnosis with advanced-stage cancer. This condition is described below.

Cancer that first develops in the lungs is classified as either small cell lung cancer or NSCLC, depending on the relative size of the cancer cells when viewed under a microscope.[2] As the name suggests, cancer cells of small cell lung cancer appear small and round under a microscope, whilst NSCLC cancer cells are larger.[3]

NSCLC is also classified by the presence of changes to specific genes within the cancer cells.[4] A genetic change that occurs in 1–2% of NSCLC cases is the joining together, or 'fusion', of a gene named '*RET*' with another independent gene.[5] This genetic change drives growth of the tumour.

For the purposes of treatment, lung cancers can be classified further by the presence of 'biomarkers', which are proteins present on the tumour. Of particular relevance to the treatment

of NSCLC is the presence or absence of the programme death-ligand 1 (PD-L1) biomarker, which is described further in section 2c) Current treatment options:

How many people have the condition

Lung cancer is the second most common cancer in England, accounting for approximately 12% of all new cancer cases, with 40,168 people newly diagnosed with lung cancer in England in 2019.[6] NSCLC accounts for the majority (80–85%) of lung cancer cases in the UK, with 70% presenting with advanced disease.[2,7] *RET* fusion-positive NSCLC accounts for approximately 1–2% of NSCLC cases equating to approximately 250 patients.[5]

Main symptoms of the disease

Common symptoms associated with NSCLC include fatigue, loss of appetite, respiratory problems, pain and coughing (which may include coughing up blood).[6] Since these symptoms are common and can be mistaken for other conditions, NSCLC is often diagnosed at advanced stages, which is when cancer that originated in the lung has spread to multiple organs. Late stage diagnosis of patients with NSCLC has been exacerbated in recent years by the COVID-19 pandemic due to the overlap in symptoms, including persistent cough and breathlessness, causing many patients with early-stage disease to self-isolate believing they have COVID-19, instead of seeking medical attention as well as patients being misdiagnosed by their doctor due to the high prevalence of the COVID-19 virus.[8]

Disease burden

People diagnosed with advanced disease have a significantly reduced chance of survival: around 57% of people diagnosed at the early stages of disease will survive for five years or longer, whilst only 3% of those diagnosed with advanced disease will survive as long.[9] On top of the physical disease symptoms, people with this condition experience anxiety and depression due to the impact of diagnosis, conversation around the disease, impact of treatment and predicted course of the disease.[10] Symptoms get worse as the disease develops, making people with NSCLC increasingly unable to complete normal activities. The quality-of-life impact for people with the condition is therefore considerably lower than in the general population.[11]

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 symptoms of NSCLC will receive an imaging scan, such as a chest X-ray, computerised tomography (CT) scan or magnetic resonance imagining (MRI) scan, which will look at the area around the lungs in order to identify if there are any abnormalities and to see if the cancer has spread. If lung cancer is suspected, patients may be asked to undergo further tests, including a biopsy, in order to identify the specific subtype of lung cancer (e.g. NSCLC) as well as any abnormal genes that might be driving the cancer (see Section 2a)).[12]

In order to identify any changes to specific genes which might be driving the cancer, patients will need to undergo genetic testing. This involves screening genetic material inside the patient's cancer cells to identify the presence of a genetic abnormality. Testing for certain abnormal genes has been routine for several years. More recently, however, the number of genes that can be tested for has expanded. To account for this expansion, a technique called Next Generation Sequencing (NGS) is currently being rolled out across the NHS. This will test for *RET* as well as all other abnormal genes in lung cancer that can be treated. NGS testing is anticipated to be adopted

across England within the next 18 months. As such, there is currently some variability in testing for *RET* in England, however NGS testing is anticipated to soon become the diagnostic standard to identify gene alterations in NSCLC.[13, 14]

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 England and Wales, guidance for the management of lung cancer is provided by the National Institute for Health and Care Excellence (NICE), via the document NG122, available here: https://www.nice.org.uk/guidance/ng122.

Further guidance on the specific types of treatment available for NSCLC is also provided by NICE via technology appraisals (TAs) documents.[15, 16]

Unmet need for a new treatment

For patients who have advanced NSCLC, systemic anti-cancer therapy is recommended by NICE, which treats cancer cells throughout the entire body. These therapies may improve symptoms and extend patients' lives, but they do not typically cure the cancer. Patients with NSCLC who have genetic changes within their cancer cells are typically treated with a systemic therapy that targets the specific genetic change. However, there are currently no targeted therapies for patients with untreated *RET* fusion-positive NSCLC that are routinely funded by the NHS. As such, these patients are currently treated with the same therapies that are used for NSCLC patients who do not have a *RET* fusion or a different genetic change in their cancer cells.

Current treatments

For advanced NSCLC patients with no identified genetic changes, NICE recommends several therapy options depending on the status of specific biomarkers in the cancer. One such biomarker is called PD-L1, which is used to classify advanced NSCLC patients into two categories: those whose PD-L1 score is 50% or more, and those whose PD-L1 score is less than 50%.

In England and Wales, the most commonly prescribed treatments for patients with advanced NSCLC are combination therapies, where several treatments are given together. These include the treatment "pembrolizumab in combination with pemetrexed" and the treatment "pemetrexed in combination with carboplatin, or platinum doublet chemotherapy (with or without subsequent pemetrexed maintenance therapy)". These treatments may be offered to all patients regardless of their PD-L1 score.[16]

Pembrolizumab is a type of 'immunotherapy', which works by using the body's immune system to kill the cancer. For patients with a PD-L1 score of 50% or more, two immunotherapy options are

recommended: pembrolizumab monotherapy or atezolizumab monotherapy.[15, 17-20] For patients with a PD-L1 score of less than 50%, atezolizumab in combination with bevacizumab, carboplatin and paclitaxel is recommended. [21]

Feedback from clinical experts is that both pembrolizumab in combination with pemetrexed (pembrolizumab combination therapy) and pemetrexed in combination with carboplatin are the most commonly used treatments in patients with advanced *RET* fusion-positive NSCLC in UK clinical practice. As such, if recommended by NICE, it is anticipated that selpercatinib will replace these therapies in UK clinical practice.

The therapies currently available to treat *RET* fusion-positive NSCLC perform poorly in terms of extending the survival of patients, with immunotherapies estimated to extend patients' lives by less than 2 years. Moreover, chemotherapies are associated with toxic side effects, reducing patients' quality of life (see Section 3f)).[10, 11]

Selpercatinib
Selpercatinib is expected to be amongst the first few options available for people with untreated *RET* fusion-positive NSCLC, and if recommended, is anticipated to fulfil a significant unmet need in England and Wales for an effective and tolerable treatment option for this condition.

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.

Global Lung Cancer Coalition, 2021 Patient Experience Survey (UK)[22]
A survey was conducted in 48 people in the UK living with lung cancer to understand their experience of living with the condition. The majority of patients (98%) had NSCLC. Over 90% of people said they were worried or depressed about the impact of lung cancer on their health, and the same proportion said they were worried about the impact of lung cancer on their family. Nearly all (around 95%) participants stated that they were or have been anxious about the potential side effects of treatment, whilst 15% declared that they never felt hopeful of positive. The survey also found that the symptoms affecting patients more seriously and causing them greater concern were fatigue, bowel problems, sleeplessness and pain.

Patient preferences for first-line treatment of metastatic NSCLC (Yong et al., 2021)[23]
A survey investigating preferences for first-line treatment of advanced NSCLC in 308 untreated and 188 caregivers was conducted. The survey found patients valued treatments that increased their survival as well as those which were not associated with side effects that may lead to hospitalisation. The survey in caregivers of patients with advanced NSCLC valued treatments which are quick to administer and have low frequency of administration.

Patient preferences for first-line treatment of metastatic NSCLC (MacEwan et al., 2020)[24]

A US study conducted in 199 people with NSCLC, the majority (80%) of whom were diagnosed with advanced disease, investigated patient preferences for first-line treatment. Overall, more than half (53.2%) of patients indicated a preference for treatment with immunotherapy alone, whilst just under a third (27.2%) of patients preferred a treatment that had both immunotherapy and chemotherapy components. The study also found patients valued a treatment option which extends survival with minimal side effects and delays to treatment initiation.

Patient-reported preference for oral versus intravenous administration for the treatment of cancer (Eek et al., 2016)[25]

A review of the scientific literature reporting patient preferences for oral compared to intravenous (i.e. treatment given via a needle directly into a vein) administration of cancer treatments (including lung cancer) found the majority (84.6%) of studies reported that patients preferred oral administration. Reasons provided included increased ease of administration and convenience due to the ability to self-administer from home.

Unmet need and value of selpercatinib

The patient-based evidence studies described above illustrate the significant unmet need that exists for an effective, targeted and tolerable treatment for advanced *RET* fusion-positive NSCLC. The clinical effectiveness of selpercatinib in patients with untreated advanced *RET* fusion-positive NSCLC has been evaluated in a large, international, multicentre clinical trial called LIBRETTO-001.[26]

The latest results of the LIBRETTO-001 trial found over 50% of patients were progression-free (i.e. their cancer had not progressed) for at least 12 months when receiving treatment with selpercatinib.[26] Clinical experts have linked progression-free survival (PFS) with overall survival (OS), suggesting that selpercatinib may have the potential to improve survival in patients with advanced NSCLC. Indeed, early survival data collected from the LIBRETTO-001 trial supports this concept.[27]

In addition, treatment with selpercatinib is associated with a tolerable safety profile, with side effects that can be easily controlled (for example with dose reductions). Moreover, selpercatinib can be taken orally, making it quicker and more convenient for patients to take than conventional infusion drugs, which require travel to infusion clinics to be administered. Selpercatinib therefore has the potential to fulfil the unmet need that exists for advanced *RET* fusion-positive NSCLC patients for an effective and tolerable treatment option with a convenient oral method of administration.

SECTION 3: The treatment

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

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

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

Selpercatinib is an anti-cancer therapy that targets cancer cells that are growing and dividing uncontrollably as a result of a *RET* gene fusion (see below).[28] It works by preventing cell growth and division in these cancer cells in order to inhibit tumour growth.

RET fusion-positive NSCLC tumours are driven by the joining together, or 'fusion', of a gene named '*RET*' with another independent gene.[5] The *RET* gene provides instructions for making a protein called 'RET' which is needed for cell growth and division.[29] When the *RET* gene becomes fused to another gene, the resulting RET protein is joined to another protein.[30] This abnormal, fused RET protein is in a permanently 'activated state', meaning that it will continue to enable the cancer cells to grow in an unregulated manner.[30] Uncontrolled cell growth and division leads to the development of tumours. Selpercatinib works by inhibiting the abnormally fused RET protein, thereby reducing levels of uncontrolled cell growth and division.

Innovation in patient care

Selpercatinib is an innovative new treatment – at present, there are no therapies routinely available on the NHS for the targeted treatment of advanced, untreated, *RET* fusion-positive NSCLC. As such, patients with this condition receive the same treatment options as those patients with no recognised genetic mutations, such as immunotherapy. OS, a measure used to indicate how long patients with cancer will live, remains poor in patients with advanced *RET* fusion positive NSCLC, with survival estimates of approximately two years or less in those treated with immunotherapy.[31] Selpercatinib is anticipated to be one of the first *RET* fusion specific treatments available for these patients.

Furthermore, the specificity of a targeted treatment such as selpercatinib is anticipated to result in better treatment results (such as prolonged survival and reduced chances of disease relapse) compared to existing non-targeted treatments. A targeted treatment interferes with particular biological drivers of the cancer, as opposed to non-targeted treatments, which may also harm healthy cells. Indeed, selpercatinib has shown meaningful treatment responses in the LIBRETTO-001 trial, reducing tumour size and increasing the period of PFS in treated patients, as explored in section 3d) Current clinical trials). In addition, the targeted nature of selpercatinib is likely to reduce side effects that result from off-target effects (side effects resulting from non-selective treatments interfering with healthy cells). The LIBRETTO-001 trial demonstrates that selpercatinib is associated with a well-tolerated, clinically manageable safety profile, with only 3.1% of patients discontinuing the drug due to side effects.[26]

Selpercatinib therefore offers the potential to satisfy an unmet need for a targeted treatment option with improved efficacy and a tolerable safety profile for patients with advanced *RET* fusion-positive NSCLC.

3b) Combinations with other medicines

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

- Yes / No

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

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

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.
No – selpercatinib is anticipated to be used as a standalone therapy and therefore does not need to be used in combination with other medicines for NSCLC.

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?
Existing treatments for untreated *RET* fusion-positive NSCLC are administered via intravenous infusion and therefore require patients to travel to dedicated infusion clinics to receive treatment.[15, 16] In comparison, treatment with selpercatinib is administered orally, twice daily via a tablet. As such, selpercatinib can be self-administered by patients at home, providing a more convenient treatment option to patients.[32] The recommended starting dose of selpercatinib is based on the body weight of the patient. For patients who weigh 50 kg (110.23 lb) or more, the recommended dose is 160 mg of selpercatinib twice a day, administered orally as 80 mg capsules (total dose per day is 320 mg). For patients who weigh less than 50 kg (110.23 lb), the recommended dose is 120 mg of selpercatinib twice a day (total dose per day is 240 mg). Capsules are also available in 40 mg dosages for patients who require a reduced dose as a result of side effects to selpercatinib.[28] Patients should take the doses at approximately the same time every day. The capsules should be swallowed whole (patients should not open, crush, or chew the capsule before swallowing) and can be taken with or without food. If a patient misses a dose of selpercatinib or vomits, they should not take an additional dose. The patient should take the next dose of selpercatinib at the scheduled time.[28] Patients are recommended to continue treatment until their cancer progresses or they experience unacceptable toxicity (e.g. unacceptable side effects), following medical advice. Further details on the administration and dosing requirements for selpercatinib can be found in the Summary of Product Characteristics (SmPC) for selpercatinib for the treatment of advanced *RET* fusion-positive NSCLC who require systemic treatment *following prior treatment with immunotherapy and/or platinum-based chemotherapy* which can be accessed via the following link: https://www.ema.europa.eu/en/medicines/human/EPAR/retsevmo#authorisation-details-section.

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 main ongoing or planned clinical trials for selpercatinib are summarised below: • **LIBRETTO-001 (NCT03157128):** A Phase I/II single arm, multicentre clinical trial evaluating the effectiveness and safety of selpercatinib in 989 patients with a variety of solid tumours. In a

single arm trial all participants receive the drug being investigated. Some (n=316) of the patients in the trial have *RET* fusion-positive NSCLC and 69 of the patients had not previously received treatment in the advanced setting.[26] The study was divided into a Phase I (dose escalation) trial, concerned with finding the most tolerable dose of selpercatinib and a Phase II (dose expansion) trial, assessing the effectiveness and safety of selpercatinib in patients. The study is currently at Phase II and is due to be completed in November 2023.

- **LIBRETTO-431 (NCT04194944):** A Phase III multicentre clinical trial comparing the safety and efficacy of selpercatinib in 250 patients to standard treatments (chemotherapy and immunotherapy) for patients with *RET* fusion-positive NSCLC. The trial is expected to complete in August 2025.

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 efficacy of selpercatinib has been demonstrated in the LIBRETTO-001 clinical trial, which enrolled 69 patients with advanced *RET* fusion-positive NSCLC who had not previously received treatment in the advanced setting.[26] These patients were representative of the population intended to be treated with selpercatinib in the UK.[26]

One of the clinical outcomes used to assess the efficacy of selpercatinib during the study was the objective response rate (ORR). The ORR refers to the proportion of patients whose tumour completely disappeared or partly reduced in size in response to treatment.[33] This is an important aim in the treatment of patients with NSCLC, as high tumour response rates are associated with delayed disease progression, which can improve physical symptoms and quality of life for patients. In LIBRETTO-001, treatment with selpercatinib resulted in high tumour response rates (84.1% of people), thus decreasing tumour size in the majority of patients.[26]

The LIBRETTO-001 study also assessed the duration of response (DOR), PFS and OS of patients treated with selpercatinib. The high response rates observed with selpercatinib treatment were shown to be durable in a large proportion of *RET* fusion-positive NSCLC patients who took part in the study, with the average DOR lasting 20.2 months. The durability of response aligned with a prolonged PFS in patients treated with selpercatinib. PFS refers to the length of time during and after treatment in which the patient's cancer does not worsen.[33] Results from the LIBRETTO-001 trial found 70.6% of patients remained progression-free at one year after starting treatment with selpercatinib.[26] In addition, although the LIBRETTO-001 trial is still ongoing and there is limited information relating to the OS of patients treated with selpercatinib, improvements observed in the PFS of patients are likely to translate to improvements in OS. Indeed, early results indicate that selpercatinib improves patient survival, with 92.7% of treated patients observed to be alive at one year and 69% alive at 2 years from treatment in LIBRETTO-001.[26]

Finally, as the LIBRETTO-001 trial was a single arm trial and therefore did not directly compare selpercatinib to existing treatments in UK clinical practice, an indirect treatment comparison (ITC) was performed for the NICE evaluation. An ITC enables the outcomes of a trial for one drug to be compared to the outcomes of a trial for another drug, in order to assess the relative effectiveness

of one drug over another. The result of this analysis showed treatment with selpercatinib led to significant improvements in response rates to treatment (ORR), time without disease progression (PFS) and survival (OS) compared to existing treatment with pemetrexed plus platinum based chemotherapy, with or without pembrolizumab.

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.

The quality-of-life impact for patients receiving selpercatinib was also assessed in the LIBRETTO-001 clinical trial. Quality of life was measured using a questionnaire that was completed by patients at multiple time points before, during and at the end of the trial. The questionnaire that was used in LIBRETTO-001 is called the European Organisation of Cancer Research Quality of Life Questions C30 (EORTC QLQ-C30).[34] This questionnaire evaluates several areas that impact the quality of life of patients with cancer, including physical, emotional, cognitive and social functioning, as well as symptoms and financial status.[34]

In most of the quality-of-life areas assessed using the questionnaire, a higher proportion of patients with advanced *RET* fusion-positive NSCLC experienced improved or stable, rather than worsening, quality of life following treatment with selpercatinib.[35] As a result, treatment with selpercatinib may help to improve and prolong quality of life for patients by delaying progression of the cancer and thus preventing the associated worsening of disease symptoms.

In comparison, patients receiving chemotherapy for NSCLC (the current standard of care for this population) typically show reduced quality of life scores following treatment. This is due to the associated toxicity of treatment caused by the lack of targeted action of chemotherapy.[36] A study in 58 patients with NSCLC receiving chemotherapy found that overall quality of life decreased significantly from 100 to 91 (p=0.03) following two rounds of chemotherapy.[37] Increased pain, decreased physical activity and increased ease of getting sick were key areas contributing towards patients decreased quality of life following treatment with chemotherapy.[37]

In addition, selpercatinib is administered orally rather than intravenously like some of the commonly used chemotherapies and immunotherapies.[32] This means that self-administration at home is possible, which is more convenient for patients, thus reducing the disease burden.

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 SmPC for selpercatinib reports side effects which are categorised as very common (occurring in more than 1 in 10 people) and common (occurring in more than 1 in 100 but less than 1 in 10 people). Very common side effects associated with selpercatinib include: decreased appetite, headache, dizziness, QT interval prolongation (an extended time between contraction and relaxation of the heart), hypertension (high blood pressure), abdominal pain, diarrhoea, nausea, vomiting, constipation, dry mouth, rash, pyrexia (fever), oedema (a build-up of fluid in the body causing swelling), increase in alanine transaminase (ALT) and aspartate aminotransferase (AST) (values related to liver health), decreased platelets, decreased lymphocyte (white blood cells) count, decreased magnesium, decreased creatinine and haemorrhage (internal or external blood loss). The only common side effect associated with treatment with selpercatinib is hypersensitivity (an immune reaction such as those caused by allergies). Both very common and common sides effects were found to be easily managed by either stopping treatment with selpercatinib or reducing the dose of selpercatinib given to patients.[28]

The safety of selpercatinib was assessed in all patients enrolled in the LIBRETTO-001 clinical trial, as well as specifically in those patients with *RET* fusion-positive NSCLC who had not previously received any anti-cancer therapies.

Overall, selpercatinib was well-tolerated by all patients studied in LIBRETTO-001. The most common side effects were oedema (a build-up of fluid in the body causing swelling), diarrhoea, fatigue, ALT increase and AST increase (values related to liver health). These side effects were easily reversed by either temporarily stopping treatment, reducing the dose of selpercatinib or treating the side effect with another medication. As a result, permanent discontinuation of selpercatinib due to side effects was uncommon (9.6%) in the LIBRETTO-001 trial. This means patients can consistently benefit from the highly effective anti-tumour activity of selpercatinib without having to discontinue treatment due to side effects.[26]

These data showed that selpercatinib provides a well-tolerated alternative to current treatment options, such as chemotherapies which are associated with toxic side effects (see Section 3f)).[38] The targeted nature of selpercatinib, as described in Section 3a), means it is able to induce high tumour response rates whilst reducing the risk of side effects compared to non-targeted therapies. As such, selpercatinib fills an unmet need for an effective, safe and tolerable treatment for patients with *RET* fusion-positive NSCLC.

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

Improved efficacy

People with NSCLC typically have poor survival, with only 3% of people diagnosed at advanced stages typically surviving five years or longer.[9] At present, there are no therapies routinely available on the NHS for the targeted treatment of advanced, untreated, *RET* fusion-positive NSCLC. If recommended, selpercatinib will be one of the first *RET* fusion specific treatments available for these patients. Due to its targeted nature, selpercatinib is anticipated to result in

better treatment results compared to existing non-targeted treatments (section 3a) How does the new treatment work?. Targeted therapies for other genetic abnormalities have transformed the outcomes of patients with certain genetic drivers.[39, 40] The potential for selpercatinib to do the same in *RET* fusion-positive patients is supported by data from the LIBRETTO-001 trial, where selpercatinib has shown to result in a good tumour response, reducing the size of the tumour in the majority of patients, as well as inducing a durable response and prolonged progression free survival. The improvements observed in PFS are likely to result in improvements in OS. Indeed, early results further indicate that selpercatinib improves patient survival (Section 3d) Current clinical trials).

Tolerable safety profile

Existing treatments for the management of advanced *RET* fusion positive NSCLC are associated with serious side effects. Notably, side effects from non-targeted immunotherapies can affect multiple different organ systems; serious side effects have been shown to occur in 7–13% of people treated with immunotherapies.[41] Moreover, chemotherapies are associated with serious side effects including oedema, diarrhoea and fatigue.[38] These side effects can have a detrimental impact on the quality of life of patients (see Section 3f)). In contrast, owing to its targeted mechanism of action (Section 3a)), the results of LIBRETTO-001 found selpercatinib to have a tolerable safety profile with manageable side effects.[26]

The improved efficacy and safety of selpercatinib compared to existing treatments is anticipated to translate to improvements in patients' quality of life. Data collected using a quality of life assessment tool as part of LIBRETTO-001 found selpercatinib treatment to result in improvements in physical, emotional, cognitive and social functioning scores, as well as symptom and financial status scores.

Convenient administration

Further to this, selpercatinib is administered orally, rather than intravenously like some of the commonly used chemotherapies and immunotherapies. This means that self-administration at home is possible, which is often preferable for patients due to its more convenient method of administration (section 2d) Patient-based evidence (PBE) about living with the condition.[25]

Finally, patients and society at large may benefit from the introduction of targeted treatments such as selpercatinib to clinical practice, as it may encourage the deployment of Genomic Hubs for genetic testing of cancers in England. In turn, this will enable more people to receive the necessary genetic testing in a timely manner, enabling access to targeted treatment without delay. Early receipt of treatment increases the chance of survival, particularly in the advanced stage of NSCLC where progression is rapid.[42, 43]

Overall, selpercatinib has the potential to satisfy the unmet need amongst patients with *RET* fusion-positive advanced NSCLC for a targeted treatment option offering both improved efficacy and tolerability profile compared to current options, as well a convenient oral method of administration.

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

Whilst selpercatinib has the potential to satisfy an unmet need amongst patients with *RET* fusion-positive NSCLC, potential disadvantages of treatment could include the frequency of administration and the requirement for additional monitoring.

Selpercatinib requires more regular administration than existing treatments in clinical practice (pembrolizumab with pemetrexed and platinum chemotherapy, and pemetrexed plus platinum combination therapy) which are administered via intravenous infusion. Selpercatinib should be administered orally as an 80 mg capsule, twice daily (section 3c) **Administration** and dosingIn contrast, pembrolizumab with pemetrexed and platinum chemotherapy is administered intravenously every 3 weeks for four 21-day cycles.[44] Pemetrexed is administered intravenously on the first day of each 21-day cycle, followed 30 minutes later by cisplatin infused over 2 hours.[44] Caregiver preference studies found caregivers of patients with NSCLC valued treatments which have a lower frequency of administration and are quick to administer, and patient preference studies revealed patients prefer oral therapies over IV due to their increased convenience and ease of administration (section 2d) Patient-based evidence (PBE) about living with the condition.[25] These studies suggest that whilst the frequent administration requirements of selpercatinib may be somewhat of a disadvantage, its quick, oral method of administration has the potential to be of benefit both patients and their caregivers.

Another potential disadvantage of treatment with selpercatinib is that it requires additional monitoring to existing treatments in clinical practice. Specifically, electrocardiograms (ECGs) and serum electrolytes should be monitored in all patients after 1 week of treatment and at least monthly for the first 6 months and otherwise, as clinically indicated. The frequency of monitoring should be adjusting based upon patients' risk factors including diarrhoea, vomiting, and/or nausea.[28]

The SmPC for selpercatinib reports side effects which are categorised as very common (occurring in more than 1 in 10 people) and common (occurring in more than one in a hundred but less than one in ten people). Very common side effects associated with selpercatinib include; decreased appetite, headache, dizziness, QT interval prolongation (an extended time between contraction and relaxation of the heart), hypertension (high blood pressure), abdominal pain, diarrhoea, nausea, vomiting, constipation, dry mouth, rash, pyrexia (fever), oedema (a build-up of fluid in the body causing swelling), increase in alanine transaminase (ALT) and aspartate aminotransferase (AST) (values related to liver health), decreased platelets, decreased lymphocyte (white blood cells) count, decreased magnesium, decreased creatinine and haemorrhage (internal or external blood loss). The only common side effect associated with treatment with selpercatinib is hypersensitivity (an immune reaction such as those caused by allergies). Both very common and common sides effects associated with selpercatinib were found to be easily managed by either stopping treatment or reducing the dose of selpercatinib given to patients.[28] Overall, selpercatinib treatment is associated with a manageable profile due to its targeted mechanism of action, which reduces side effects caused by off-target effects (when a drug affects another pathway in the body in addition to the intended target). In addition, the adverse effects associated with selpercatinib are less severe than those associated with alternative treatments, such as existing chemotherapies.

3j) 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.

Selpercatinib meets an urgent, unmet need for an effective treatment option, with a tolerable safety profile and convenient method of administration for patients with advanced, untreated *RET* fusion-positive NSCLC.

Clinical value of selpercatinib

The results of the LIBRETTO-001 trial found treatment with selpercatinib resulted in a good tumour response, with tumour size decreasing in the majority of patients. This response was found to be maintained over time, with patients demonstrating a prolonged duration of response. The durability of response aligned with a prolonged PFS in patients treated with selpercatinib, with a median time without disease progression (PFS) of 22 months.[26] These benefits in PFS are likely to translate into benefits in patients survival (OS), with 92.7% of people expected to be alive at one year from the start of treatment, 69.3% at two years and 57.1% at three years.[26] The EORTC QLQ-C30 found that in most of the quality-of-life areas assessed using the questionnaire, a higher proportion of patients with advanced *RET* fusion-positive NSCLC experienced improved or stable, rather than worsening, quality of life following treatment with selpercatinib.[35]

As the LIBRETTO-001 trial was a single arm trial and therefore did not directly compare selpercatinib to existing treatments in UK clinical practice, an indirect treatment comparison (ITC) was performed. An ITC enables the outcomes of a trial for one drug to be compared to the outcomes of a trial for another drug, in order to assess the relative effectiveness of one drug over another. The ITC conducted for selpercatinib compared data from LIBRETTO-001 to data obtained from trials for treatments that represent current standard of care in the UK clinical practice; namely pembrolizumab combination therapy and pemetrexed plus platinum-based chemotherapy. The result of this analysis showed treatment with selpercatinib led to significant improvements in response rates to treatment (ORR), time without disease progression (PFS) and survival (OS) compared to pemetrexed plus platinum based chemotherapy with or without pembrolizumab.

Economic analysis

An economic analysis was performed to assess whether selpercatinib represents good value for money and a good use of resources for the NHS compared to existing treatments in UK clinical practice. The analysis was performed using an economic model. In order to capture all of the potential costs and benefits associated with treatment with selpercatinib, the model assessed the cost-effectiveness of selpercatinib over the lifetime of patients with advanced NSCLC. The economic model itself was comprised of three health states: progression free (patients' disease is responding to treatment and not actively progressing), progressed (the patient's cancer has worsened) and death, reflecting the three potential stages of health associated with advanced NSCLC. The model did not allow patients to move to an improved level of health, reflecting the progressive nature of the disease.

The PFS and OS results of the ITC described above were the main clinical inputs in the economic analysis. As the ITC was informed by clinical data from the relevant trials of selpercatinib and its comparators the model is expected to accurately reflect disease progression and the survival rate of patients treated with these therapies in UK clinical practice. As data obtained from the LIBRETTO-001 trial was limited to two years, these data were extrapolated in order to cover the full lifetime horizon of the economic model (25 years). Survival curves selected for the extrapolations were informed by UK clinical experts to ensure they accurately reflected the natural progression of the disease.

Due to the improved efficacy of selpercatinib compared to existing treatments it is anticipated that patients will remain progression-free for longer (and hence remain in the progression-free health state of the model for longer). Patients whose disease has not yet progressed have improved health-related quality of life compared to patients whose disease has progressed due to the associated worsening in symptoms with disease progression.[11]

Due to the increased time spent in PFS for patients treated with selpercatinib versus the comparators, owing to its improved efficacy compared to other treatments, the costs to the NHS associated with treating patients whose disease has progressed, such as increased hospital visits, are reduced. The costs to the NHS associated with treatment administration are also reduced compared to the comparator treatment regimens, which require IV administration.

Overall, the economic analysis showed selpercatinib to be a good use of NHS resources as a new treatment option for untreated patients with *RET* fusion-positive NSCLC, when considering the trade-off between the costs and health benefits associated with selpercatinib compared with currently available treatments. Typically NICE considers a willingness-to-pay threshold of ~£30,000 for every year of perfect health (called a quality-adjusted life year or QALY) but because of the severity of advanced *RET* fusion-positive NSCLC, a higher willingness-to-pay threshold of £36,000 was assumed. Compared with pemetrexed plus platinum based chemotherapy and pembrolizumab combination therapy, the results of the economic analysis showed selpercatinib to provide one QALY for a cost of £35,883 and £5,264, respectively. As these costs are below the threshold of £36,000, it is anticipated that selpercatinib will represent a good use of NHS resources, however these results are yet be evaluated by NICE.

The results of the economic analysis were analysed in several sensitivity and scenario analyses, which varied the inputs and assumptions used in the economic model. The analyses found the results of the economic model to be robust to variations in model inputs and assumptions, however these results are yet to be evaluated by NICE.

Additional value of selpercatinib

A notable benefit of selpercatinib is that it has a convenient oral method of administration. Current alternatives to selpercatinib in UK clinical practice require intravenous infusion and therefore need to be administered by a nurse in a hospital, resulting in a greater economic burden on NHS resources.

In addition, owing to its targeted mechanism of action, selpercatinib is associated with a tolerable safety profile, unlike current clinical management, which is often associated with off-target side effects that require treatment, resulting in increased resource use and expenditure by the NHS.

3k) 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)

Targeted treatment

There are currently no targeted therapeutic options recommended by NICE for the treatment of advanced untreated *RET* fusion-positive NSCLC that are routinely funded by the NHS. Selpercatinib is expected to be one of the first in its class as a targeted treatment option for these patients. Currently, advanced, untreated, *RET* fusion-positive NSCLC patients are treated with the same treatments used for patients without recognised genetic changes that cause NSCLC, including pemetrexed plus platinum based chemotherapy and pembrolizumab combination therapy. These treatments are not targeted at *RET* fusion-positive NSCLC and therefore are associated with sub-optimal outcomes. Progression-free survival in untreated *RET* fusion-positive NSCLC patients treated with pemetrexed plus platinum chemotherapy or pembrolizumab combination therapy has been reported to be only 6.4 months and 6.6 months, respectively. Selpercatinib has shown high selectivity for *RET* and consequently is likely to improve clinical outcomes for untreated *RET* fusion-positive NSCLC patients. The LIBRETTO-001 study in untreated *RET* fusion-positive NSCLC patients treated with selpercatinib has shown progression-free survival to last over twice as long (22 months).[27]

Tolerable safety profile

In addition to its improved clinical outcomes, due to its targeted mechanism of action, selpercatinib is associated with an improved safety profile and more manageable side effects compared to existing therapies, due to the reduction in off-target side effects (side effects resulting from non-selective treatments interfering with healthy cells). Side effects from non-targeted immunotherapies can affect multiple different organ systems; serious side effects have been shown to occur in 7–13% of people treated with immunotherapies.[41] Treatment with chemotherapies are associated with severe side effects, affecting one or several different organ systems. In contrast, selpercatinib is well tolerated, with side effects that can be easily reversed by reducing dosage.[5] Results from the LIBRETTO-001 trial demonstrate that selpercatinib is associated with a well-tolerated, clinically manageable safety profile, with only 3.1% of patients discontinuing treatment due to side effects associated with selpercatinib.[26]

Convenient administration

Finally, in comparison to existing treatments in clinical practice, selpercatinib is administered orally.[15, 16, 28] Existing treatments for untreated *RET* fusion-positive NSCLC are administered via intravenous infusion. A review of the scientific literature reporting patient preferences for oral compared to intravenous administration of cancer treatments (including lung cancer patients) found the majority (84.6%) of studies reported a patient preference for oral administration (see

Section 2d)).[25] Reasons provided included increased ease of administration and convenience due to the ability to self-administer from home.[25] In addition, a survey investigation the preferences of caregivers of patients with advanced NSCLC found caregivers prefer treatments that are quick to administer, thus showing selpercatinib fulfils an unmet need for a convenient oral treatment.[23]

Overall, selpercatinib is an innovative new treatment for untreated *RET* fusion-positive NSCLC, representing a step change in its levels of effectiveness, improved safety and convenient oral method of administration.

3l) 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

It is not expected that treatment with selpercatinib will result in any equality issues when considering untreated *RET* fusion-positive NSCLC. Any groups of people with *RET* fusion-positive NSCLC would be protected by equality legislation and it is not expected that any recommendation of selpercatinib would have a different impact on people protected by equality legislation than on the wider population of *RET* fusion-positive NSCLC patients.

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 the content covered in this document:

- NICE Guideline for the diagnosis and management of lung cancer – NG122: https://www.nice.org.uk/guidance/ng122
- Summary of Products Characteristics (SmPC) for selpercatinib for the treatment of patients with advanced RET fusion-positive NSCLC who require systemic treatment following prior treatment with immunotherapy and/or platinum-based chemotherapy: https://www.ema.europa.eu/en/medicines/human/EPAR/retsevmo#authorisation-details-section
- Cancer Research UK – Lung Cancer: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types#:~:text=Around%2080%20to%2085%20out,treatment%20in%20a%20similar%20way
- ClinicalTrials.Gov information on LIBRETTO-001 – NCT03157128: https://clinicaltrials.gov/ct2/show/NCT03157128

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

Glossary

Term	Definition
Biomarker	A biological indicator, such as a gene, a protein or a molecule, which indicates a specific disease or process
Chemotherapy	A type of cancer therapy that uses drugs to kill cancer cells
Fusion	The joining together of two genes
Gene	A unit of genetic material that contains the information to make a protein
Genetic mutation	An alteration of the normal gene
Immunotherapy	A type of cancer therapy that uses the body's own immune system to fight cancer
Marketing authorisation	The authorisation given by a regulatory body (such as the EMA or MHRA in the UK) to put the drug on the market
Metastatic	Cancer that has spread to other parts of the body beyond its original origin
Radiotherapy	A type of cancer therapy that uses radiations to kill cancer cells
Systemic therapy	A type of cancer therapy that is aimed at the whole body or multiple organs, not just at a specific location
Targeted therapy	A type of therapy that targets a specific characteristic of the cancer, such as a genetic mutation
Untreated	Patients who have never received any treatment for their tumour

Abbreviations

Acronym	Abbreviation
DOR	Duration of response
EORTC QLQ-C30	European Platform of Cancer Research Quality of Life Questions C30
HTA	Health Technology Assessment
ITC	Indirect treatment comparison
MHRA	Medicine and Healthcare Products Regulatory Agency
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBE	Patient-based evidence
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
RET	Rearranged during transfection

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:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]
Clarification questions

25th October 2022

File name	Version	Contains confidential information?	Date
ID4056_Selpercatinib untreated RET NSCLC clarification questions response to NICE [Redacted]_25.10.22	Final	Yes	25.10.2022

Section A: Clarification on clinical effectiveness data

Literature Searches

A1. Why were the search strategies used for the final two clinical evidence update searches, SLR4 and SLR5 (Appendix D), different to the previous clinical evidence search strategies, SLR1, SLR2, SLR2 targeted, SLR3 and SLR3b (Appendix D)?

a) For the population facet the earlier strategies searched for NSCLC, while the final two strategies searched for '(Lung cancer OR NSCLC) AND (advanced OR metastatic) AND (first line therapy OR untreated) AND (RET fusion OR RET oncogene)'

b) A different RCT search filter was used in the final two clinical evidence update searches.

c) An age limit for 'adults' was included in the final two clinical evidence update searches, and not in the previous searches.

SLR1 and SLR2 were conducted from a Global perspective, with objectives and scope broader than the current decision problem. From SLR3, the search strategy was narrowed to make it more robust and specific; the addition of the search terms and age limits reduced the number of irrelevant hits produced. Fundamentally, the search strategy remained broadly similar throughout all of the relevant updates, but with amendments made for the last two updates to make them specific, directed and optimised for the population of interest. Lilly do not consider that these adjustments will have excluded any relevant data from the search results.

A2. Please provide full details of the search strategies for the clinical trial registries searches (ClinicalTrials.gov and International Clinical Trials Registry Platform) reported in Appendix D.1.1, including the date searched and number of records retrieved.

Details of the search strategy for ongoing trials, including search criteria and limitations, implemented in SLR4 and SLR5 are presented in Table 1. Searches were conducted on 30th July and 3rd August 2021 for SLR4, and on 3rd June 2022 for SLR5. Since the evidence was being sourced from grey literature, the numbers of records retrieved were not recorded.

Details of clinical trial registry searches are not available for SLR1–3.

Table 1. Search strategy of ongoing trials SLR4/SLR5

Search Criteria	Limitations
Clinical trials registries	• International Clinical Trials Registry Platform • Clinicaltrials.gov
Patients, comparators, and outcomes	The keywords used for identifying relevant ongoing clinical trials were “lung cancer”, “non-small cell lung cancer”, and “studies with results”
Recruitment status	Open studies: • Recruiting • Not yet recruiting • Expanded access: available • Enrolling by invitation Closed studies: • Active, not recruiting • Completed Studies with Unknown Status will not be included
Results	Studies with available results (Studies without results will be excluded)

Abbreviations: SLR: systematic literature review.

A3. Please provide full details of the searches of health technology assessment organisations referred to in Appendices D.1.1 and G.2 including the resources searched, the search strategies or search terms used, and results.

In Appendix D.1.1, for the searches of health technology assessment organisations, the National Institute for Health and Care Excellence (NICE) UK website (https://www.nice.org.uk/) was hand searched for published assessments and guidelines.

Details of the HTA resources searched, search strategies or search terms used, and results, as referred to in Appendix G.2 are presented in Table 2 below.

In addition, NICE website searches for “non-small cell lung cancer” were performed for SLR4 and SLR5 on 29th July 2021 and 1st June 2022, respectively. Details of NICE website searches are not available for SLR1–3.

Table 2. Health technology assessment organisations searched

Website/Database/ Register Searched (Name, Address)	Indication	Date of Search	Search Terms Used	Details/Limits	Number of Records	Number of Potentially Relevant Articles
University of York's Centre for Research and Dissemination: https://www.crd.york.ac.uk/CRDWeb/	NSCLC	7 October 2019	"non-small cell lung cancer" AND ("cost" OR "economic")	Published in 2015 onwards	2	2
Tufts Medical Center Cost-Effectiveness Analysis (CEA) Registry: http://healtheconomics.tuftsmedicalcenter.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx	NSCLC	7 October 2019	non-small cell lung cancer	Published in 2015 onwards	36	36
The Institute for Clinical and Economic Review (ICER): https://icer-review.org/	NSCLC	8 October 2019	non-small cell lung cancer	Published in 2015 onwards	12	1
National Institute for Health and Care Excellence (NICE), United Kingdom (UK): https://www.nice.org.uk/	NSCLC	8 October 2019	non-small cell lung cancer	As specified in the protocol	1	1
Scottish Medicine Consortium (SMC): https://www.scottishmedicines.org.uk/	NSCLC	8 October 2019	non-small cell lung cancer	Published in 2015 onwards	26	8
Canadian Agency for Drugs and Technologies in Health (CADTH): https://www.cadth.ca/	NSCLC	8 October 2019	non-small cell lung cancer	Published in 2015 onwards	121	14
Total					**198**	**62**

Abbreviations: CADTH: Canadian Agency for Drugs and Technologies in Health; CEA: Cost-effectiveness analysis; ICER: Institute for Clinical and Economic Review; NSCLC: non-small cell lung cancer; SMC: Scottish Medicines Consortium.

A4. Please provide full details of the searches of conference proceedings referred to in Appendix G.2 including the resources searched, the search strategies or search terms used, and results.

Searches of conference abstracts were limited to proceedings published from 2017 to present given that it was expected that all articles of a reasonable quality reported in abstract form before this date would have been published in a peer-reviewed journal. Therefore, any abstracts before 2017 found in the Internet searches were excluded.

Abstracts from the following conferences were of interest:

- International Society for Pharmacoeconomics and Outcomes Research: http://www.ispor.org/heor-resources/presentations-database/search
- American Society of Clinical Oncology (ASCO) (http://www.asco.org/)
- European Society for Medical Oncology (ESMO) (http://www.esmo.org/)
- International Association for the Study of Lung Cancer (IASLC) (https://www.iaslc.org/)

As they were all indexed in Embase, these websites were not searched.

A5. Please provide the missing lines from the clinical evidence SLR5 MEDLINE search strategy (Appendix D, Table 8).

Lilly apologise that lines were missing from the clinical evidence SLR MEDLINE search strategy. The full search strategy is presented in Table 3.

Table 3. Ovid MEDLINE search strategy for first line clinical trial evidence in NSCLC. Search conducted on 20th April 2022 (SLR5)

Search number	Search terms	Hits
#1	exp lung neoplasms/	259348
#2	(non-small cell lung cancer or nonsmall cell lung cancer or NSCLC or nonsmall-cell lung cancer or non-small-cell lung cancer).tw,kw.	77568
#3	((Lung or bronchial or pulmonary) and (non-small-cell or nonsmall-cell or non-small cell)).tw,kw.	77877
#4	((lung$ or bronch* or pulmonary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	266867
#5	1 or 2 or 3 or 4	350128
#6	(metasta* or advanced or stage IIIB or stage IV or stage 4 or stage four).tw,kw.	1022120
#7	5 and 6	105853
#8	(first line therapy or first-line or first line or 1st line or untreated or treatment naive or previously untreated or first-line to progression or first line to progression).tw,kw.	292633
#9	7 and 8	7932

#10	(selpercatinib or LY3527723 or LY-3527723 or LY 3527723 or LOXO-292 or LOXO 292 or LOXO292 or RETEVMOTM or RETEVMO TM or RETSEVMO or Pralsetinib or blue-667 or blue 667 or blue667 or blu 667 or blu-667 or blu667 or cs-3009 or cs 3009 or cs3009 or gavreto or RET inhibitor or RET inhibitors).mp.	301
#11	*cisplatin/	23409
#12	(Cisplat$ or abiplatin or bioc#splatinum or blastolem or briplatin or cddp ti or cis ddp or (cis adj2 dichloroplatinum) or cis diamin#chloroplatinum or (cis adj2 platinum) or cis plat$ or cytoplatin or cytosplat or diamine dichloroplatinum or diam?in#dichloroplatinum or dichlorodiam?ineplatinum or dichlorodiam?ine platinum or Docistin or elvecis or Kemoplat or lederplatin or Lipoplatin or mpi 5010 or mpi5010 or Neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or Platimine or platinex or Platinil or platinol or (platinum adj2 diaminodichloride) or Platinum diam?in#dichloride or (platinum adj2 dichloride) or Platiran or platistil or Platistin or platosin or Randa or romcis or Sicatem or "spi 077" or Tecnoplatin).mp.	84971
#13	*carboplatin/	3576
#14	(Carboplat$ or blastocarb or boplatex or carbosin or carbotec or carplan or CBDCA or cycloplatin or erbakar or ercar or ifacap or jm 8 or kemocarb or nsc 241240 or oncocarbin or paraplatin$ or nealorin or neocarbo or platinwas or ribocarbo).mp.	19605
#15	*gemcitabine/	0
#16	(Gemcitabine or gemcite or gemzar or ly 188011 or ly188011).mp.	19285
#17	*docetaxel/	898
#18	(docetaxel or daxotel or dexotel or docefrez or docetaxel accord or lit 976 or lit976 or n debenzoyl n tert butoxycarbonyl 10 deacetyltaxol or n tert butoxycarbonyl 10 deacetyl n debenzoyltaxol or nsc628503 or nsc 628503 or oncodocel or rp 56976 or rp56976 or taxespira or taxoter$ or taxotere or texot or taxoltere metro).mp.	18732
#19	*pemetrexed/	362
#20	(pemetrexed or alimta or armisarte or ciambra or elimta or ly 231514 or ly231514 or ly 231 514 or MTA or pemfexy or pemta).mp.	8839
#21	*paclitaxel/	15041
#22	(paclitaxel or "abi 007" or abraxane or anzatax or asotax or biotax or bms 181339 or bms181339 or bristaxol or britaxol or coroxane or Formoxol or genexol or hunxol or ifaxol or infinnium or intaxel or medixel or mitotax or nsc 125973 or nsc125973 or oncogel or onxol or pacitaxel or pacxel or padexol or parexel or paxceed or paxene or paxus or praxel or taxocris or taxol or taxus or taycovit or yewtaxan).mp.	45433
#23	*bevacizumab/	2956
#24	bevacizumab or altuzan or avastin or nsc 704856 or nsc704865).mp.	21049
#25	*erlotinib/	788
#26	(erlotinib or Tarceva or nsc 718781 or nsc718781 or osi 774 or osi774 or r 1415 or r1415 or cp 358774 or cp358774).mp.	7588
#27	*ramucirumab/	0
#28	(ramucirumab or cyramza or imc 1121 or imc 1121b or imc1121 b or imc1121b or ly 3009806 or ly3009806).mp.	1092
#29	*nivolumab/	1773
#30	(nivolumab or bms 936558 or bms936558 or cmab819 or cmab 819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).mp.	7977
#31	*gefitinib/	364

#32	(Gefitinib or geftinat or iressa or zd 1839 or zd1839).mp.	8124
#33	*afatinib/	239
#34	(Afatinib or bibw 2992 or bibw2992 or gilotrif or tovok or giotrif).mp.	1853
#35	*crizotinib/	332
#36	(Crizotinib or "pf 02341066" or pf 1066 or pf 2341066 or pf02341066 or pf1066 or pf2341066 or xalkori).mp.	3015
#37	*pembrolizumab/	0
#38	(Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475 or sch900475 or sch900475).mp.	7115
#39	*ipilimumab/	669
#40	(ipilimumab or bms 734016 or bms734016 or "mdx 010" or mdx 101 or mdx010 or mdx101 or strentarga or yervoy or CTLA 4).mp.	14780
#41	*ticilimumab/	0
#42	(ticilimumab or cp 675 206 or cp 675206 or cp675 206 or cp675206 or tremelimumab).mp.	408
#43	*durvalumab/	0
#44	(durvalumab or imfinzi or medi 4736 or medi4736).mp.	1112
#45	*atezolizumab/	0
#46	(atezolizumab or mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq or tecntriq).mp.	2224
#47	or/10-46	215560
#48	9 and 47	4764
#49	(juvenile or juvenile* or infant or child* or adolescen* or teen*).mp.	4356383
#50	(adult or adults or above 19 years or >19 years or above 18 years or >18 years or aged or middle aged).mp.	8721030
#51	49 not 50	2156965
#52	(crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure or random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer*).mp.	2131424
#53	(single arm or single-arm or one arm or one-arm or clinical study or clinical stud* or clinical trial* or phase 2 clinical trial or prospective study).mp.	1385202
#54	52 or 53	2986019
#55	animal/ not (animal/ and human/)	4962782
#56	(comment* or letter or editorial or note or short survey or conference review or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	4032571
#57	55 or 56	8228094
#58	(RET mutation or RET-mutation or RET mutant or RET-mutant or RET fusion or RET-fusion or RET proto oncogene or RET proto-oncogene or rearranged during transfection or oncogene RET or RET oncogene or c RET protein or c RET protein or c RET receptor tyrosine kinase or c RET tyrosine kinase or protein c RET or proto oncogene protein c RET or proto oncogene proteins c RET or proto-oncogene protein c RET or proto-oncogene proteins c RET or protooncogene protein c-RET or proto-oncogene proteins c-RET or proto-oncogene protein c RET or RET protein or RET receptor tyrosine kinase or RET tyrosine kinase or RET rearrangement or RET alteration RET altered or RET aberration).mp.	4923
#59	(9 and 58 and 54) not (51 or 57)	14

#60	limit 59 to dc=20210706-20220420	1
#61	(48 and 52) not (51 or 57)	1472
#62	limit 61 to dt=20210706-20220420	101

A6. Please explain why the cost effectiveness searches reported in section B.3 and Appendix G conducted in March 2019 have not been updated.

Due to time and resource constraints, an update to this SLR could not be completed in time for submission. Lilly do not anticipate that an updated will significantly impact the current decision problem or cost-effectiveness assessment. In addition, the publication of recent NICE appraisals for selpercatinib in the second line (TA760) and pralsetinib (TA812) in a similar indication provides confidence that the most relevant information for economic modelling is already available.[1, 2]

Decision problem

A7. Priority question: The phrase "who require systemic therapy" is added to the definition of the scope population in the company's decision problem (Table 1).

a) What implications does this have for the characteristics of the patients and standard care i.e., the comparators?

This wording was added to reflect the anticipated marketing authorisation for the indication under appraisal. Lilly can now confirm that the description of the population in the decision problem should be updated to align with the anticipated label: 'Selpercatinib as a monotherapy is indicated for the treatment of adults with advanced *RET* fusion-positive NSCLC **not previously treated with a RET inhibitor'**.

b) How would those who require systemic therapy be differentiated from those who do not?

As outlined in Section B.1.2.2. of the Company Submission, *RET*-fusion positive patients are identified via genetic testing. Specifically, next generation sequencing (NGS) can be completed by Genomics Hubs, which allows a panel of genetic mutations, rearrangements and fusions (including *RET* fusions) to be identified.[3]

A8. Priority question: The company submission states that "The evidence presented in this submission is for patients with non-squamous histology." (Table 1) Please confirm whether the population in the decision problem should be amended accordingly?

As noted in Section B.1.2.1 of the Company submission, *RET* fusions are most commonly seen in adenocarcinoma, but have also been reported in mixed adenosquamous histology.[4] The relative rarity of *RET* mutations with a squamous histology is supported by a recent retrospective

observational study published by Hess 2021, which found that patients exhibiting metastatic NSCLC with *RET* mutations were more likely to have non-squamous histology than the general NSCLC population.[5] As such, whilst squamous histology was not an exclusion criterion for enrolment in the LIBRETTO-001 trial, owing to the rarity of *RET*-fusion positive squamous histology, no squamous patients were enrolled into the SAS1 population.[6]

This is reflected by the Committee conclusions in a recent NICE appraisal, TA760 for selpercatinib in previously treated *RET* fusion-positive advanced NSCLC.[7] In this submission, no evidence on the treatment of squamous tumours was presented owing to only a very small number of squamous patients enrolling in the efficacy set. However, the NICE Committee noted that the marketing authorisation for selpercatinib in this indication does not differentiate between patients with squamous and non-squamous histology. Furthermore, the Committee acknowledged that the RET-fusions positive squamous population is very small, and heard from clinical experts that [redacted].[7] As such, the Committee agreed that the recommendations [redacted].[7]

Therefore, Lilly can confirm that a broad recommendation, unrestricted by squamous histology, is being sought for selpercatinib in the first-line setting, and therefore that the population in the decision problem should not be amended from the wording currently provided.

A9. Priority question: Pemetrexed and platinum chemotherapy is included as a comparator in the company submission, despite not being included in the NICE scope for non-squamous histology. Pembrolizumab monotherapy, atezolizumab, atezolizumab plus bevacizumab and chemotherapy plus platinum (platinum doublet chemotherapy) were not included as comparators in the company submission, but were included in the NICE scope. All are included in the care pathway for RET fusion positive advanced NSCLC in NICE guideline 122 (September 2022).

a) Please provide adequate justification for these discrepancies, citing objective evidence of standard care for the non-squamous RET fusion positive advanced NSCLC population.

Pemetrexed with platinum chemotherapy is included in the NICE scope for patients with non-squamous histology. 'Pemetrexed in combination with a platinum drug (carboplatin or cisplatin)' is included in the list of comparators for patients with adenocarcinoma. As outlined in Section B.1.2.1 of the Company Submission, adenocarcinoma and large cell undifferentiated carcinoma are considered together under "non-squamous" histology.[8]

As outlined in Section B.1.2.2 of the Company Submission, comparator choice was informed by feedback received from expert oncologists practicing in the NHS to ensure only the most relevant comparators to selpercatinib in UK clinical practice were selected. The expert oncologist consulted noted that immunotherapies alone are less effective in *RET*-fusion positive patients and therefore their use in clinical practice is limited.[9] The limited efficacy of mono-immunotherapy

in these patients is supported by the conclusions of a real-world evidence study conducted by Offin *et al*. in 2019, which found median PFS in *RET*-fusion positive NSCLC patients treated with mono-immunotherapy was just 3.4 months (95% CI, 2.1 to 5.6 months).[10] The authors concluded that RET-fusion positive lung cancers may be less likely to be highly responsive to immunotherapy as compared with other cancers, and noted that this was reflected in the overall poor outcomes observed. In addition to this, the expert oncologist consulted by Lilly emphasised that UK clinicians are typically keen to avoid use of mono-immunotherapies as first line options in *RET*-fusion positive patients, particularly considering the associated toxicities that can occur if a tyrosine kinase inhibitor (TKI) is subsequently provided in the second line.[11]

Based on this, the expert feedback received from Lilly was that patients in UK clinical practice are typically treated with either pemetrexed with platinum-based chemotherapy or pembrolizumab in combination with pemetrexed plus platinum chemotherapy, as these have demonstrated improved efficacy in the *RET* fusion-positive population.[9] This feedback, and the subsequent comparator choice, is aligned with that received from clinical experts consulted as part of the recent evaluation of pralsetinib in the same indication (TA812).[2] As such, pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy are considered the only relevant comparators to selpercatinib in this indication.

b) Please conduct all effectiveness analyses, whether by indirect treatment comparison (ITC) (by using individual patient data [IPD]) or network meta-analysis (NMA) or combination (as in the company submission), and cost-effectiveness analyses including all comparators in the scope and the NICE guideline 122 care pathway.

As outlined in response to Question A.9a), Lilly consider that pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy represent the only relevant comparators to selpercatinib in this submission. As such, neither an NMA nor cost-effectiveness analysis including the other treatments named in the NICE scope have been conducted.

A10. Please justify the use of the outcome ‘duration of response’, given that this is not in the NICE scope and that it may overlap with other outcomes.

Overall response rate (ORR) was the primary endpoint in LIBRETTO-001, with objective response rate and best overall response also being measured. Improved response rate and reductions in tumour size may lead to the relief of symptoms and help to preserve HRQoL.[12] Therefore, duration of response was also considered as an important outcome because by maintaining the response of the tumour to treatment and inducing shrinkage, relief from disease progression may be maintained for longer and patients may experience improved OS.[13] However, results for this outcome were provided as supportive data only and did not inform the economic model.

A11. The European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C-30 (QLQ-C30) was chosen as the HRQoL measure.

a) Please justify the use of this measure over other cancer-specific alternatives.

The phase I/II LIBRETTO-001 study collected EORTC QLQ-C30 data to address an exploratory objective: 'To collect patient-reported outcomes (PRO) data to explore disease-related symptoms and health-related quality of life (HRQoL)". The study population was not restricted to one tumour type, like NSCLC, where more specific questionnaires would be available. EORTC QLQ-C30 is well established cancer PRO tool that is broadly used and validated, and it represents one of the most commonly used measured in cancer.[14] As such, Lilly consider the EORTC QLQ-C30 data adequately and appropriately capture HRQoL for patients in the LIBRETTO-001 trial.

b) Why was EQ-5D or another utility measure not used?

Generic measures of health, such as EQ-5D, are available and can be used to inform economic evaluation. However, they have been found to be inappropriate or insensitive for some medical conditions and for cancer in particular where it is less sensitive to cancer-specific symptoms.[15, 16] In contrast, as outlined in response to Part a) of this question, changes from baseline in disease-related symptoms and HRQoL are well addressed by the EORTC QLQ-C30.

In addition, the LIBRETTO-001 study was a Phase I/II exploratory basket trial, including other solid tumours and was therefore not designed as a randomised trial or large confirmatory trial, such as those for Phase 3. As such, collection of EQ-5D data was not included in the trial design in order to lessen the burden of data reporting for health care providers and patients. However, the LIBRETTO-431 study uses more questionaries including both EORTC QLQ-C30 and EQ-5D.[14]

Selpercatinib trials

A12. Priority question: Outcomes are presented and used in all analyses (ITC and cost-effectiveness analysis [CEA]) for the Supplemental Analysis Set 1 (SAS1) population of LIBRETTO 1. Please confirm that the patients in the SAS1 population are all the RET fusion-positive NSCLC patients that were included in LIBRETTO-001 and that there were no RET fusion-positive NSCLC patients treated in LIBRETTO-001 omitted from the SAS1 population. Otherwise, please include all RET fusion-positive NSCLC patients treated in LIBRETTO-001.

In addition to the analysis sets provided in the submission (OSAS and SAS), LIBRETTO-001 included three additional analysis sets for patients with NSCLC, including: SAS2 (patients who have received prior systemic therapy), SAS3 (patients with non-measurable disease) and IAS (patients previously treated with platinum-based chemotherapy). However, in line with the decision problem, only clinical effectiveness data from treatment-naïve patients with measurable disease were considered in the submission (SAS1). Lilly can confirm that all treatment-naïve *RET*-fusion positive NSCLC patients enrolled into the LIBRETTO-001 trial were included in the SAS1 population.

A13. Priority question: Evidence from LIBRETTO-001 is based on a 15 June data cut-off. Median OS was not estimable at this cut-off. Please provide

evidence from a later cut-off and let us know when the next data cut-off will be available.

At this current time, no data from a later data cut-off from the LIBRETTO-001 trial are available. The next data cut-off from the LIBRETTO-001 trial is anticipated to occur in [redacted], with results expected to become available in [redacted].

A14. Priority question: Section B.2.10 states: "Results for LIBRETTO-431 are expected in December 2023. It is not anticipated for any data from this trial to become available during the course of this evaluation." Please provide the earliest date by which an interim analysis might be available and for which outcomes from LIBRETTO-431 might be available?

The interim analysis will be event driven and will be conducted when approximately [redacted] events in the primary outcome, PFS by BICR, have been observed in the ITT-pembrolizumab population. It is anticipated this criterion will be met in [redacted] with results expected to be available from [redacted].

A15. Priority question: The dose of selpercatinib is given as 160 mg twice daily.

a) Was this dose amended for any participants weighing <50kg in the LIBRETTO-001 trial (as it is for other indications)? If not, please justify. If it was amended, please clarify the number of participants affected.

In LIBRETTO-001, there were [redacted] patients with weight <50 kg at baseline, all of whom received 160 mg BID. Starting doses for patients in LIBRETTO-001 are presented in Table 4 and were the doses used in the economic model. Weight was not a criterion for determining the starting dose, owing to LIBRETTO-001 being a Phase I/II study with a Phase I 'dose finding' phase which included dose escalation.

As presented in Table 32 of the Company Submission, dose reductions were primarily due to the occurrence of adverse events. Drug dosage modifications and the reasoning for these modifications in the SAS1 population of the LIBRETTO-001 trial specifically are presented in Table 5. As shown, adverse events represented the majority of reasons for modifications. A total of [redacted] patients started on a lower dose of 80 mg BID, and this was due to the Phase I 'dose finding' nature of LIBRETTO-001.

Table 4. Starting doses of patients in LIBRETTO-001

Dose (mg, twice daily), n (%)	SAS1 population ([redacted])
160	[redacted]
120	[redacted]
80	[redacted]
40	[redacted]
All	[redacted]

Abbreviations: SAS: supplementary analysis set.

Table 5. Study drug dosage modifications in LIBRETTO-001

Study drug modification type and reason, n (%)	SAS1 population ([redacted])
Any dose reduction	[redacted]
Adverse event	[redacted]
Other reasons	[redacted]
Any dose withheld	[redacted]
Adverse event	[redacted]
Other reasons	[redacted]
Any dose increase	[redacted]
Intra-patient dose escalation	[redacted]
Dose re-escalation	[redacted]
Other reasons	[redacted]

Abbreviations: SAS: supplementary analysis set.

b) Please confirm that the dosing in the economic model is the same as the LIBRETTO-001 trial. Otherwise, please describe any discrepancies and discuss the implications.

Lilly can confirm that the dosing scheduled considered in the economic model was the same as in the LIBRETTO-001 trial.

A16. Subgrouping was planned for the existence of brain metastases. Please justify the choice of this subgrouping variable in terms of how the existence of brain metastases are expected to influence the efficacy of selpercatinib.

A subgroup analysis to assess overall responses rates based on the RECIST 1.1 criteria, assessed by IRC, in patients with Investigator assessed brain metastases was performed in LIBRETTO-001. Differential efficacy of selpercatinib in this subgroup of patients was not anticipated as compared with *RET*-fusion positive patients without brain metastases, however this subgroup analysis was pre-specified owing to the high prevalence of brain metastases in patients with *RET* rearrangements, with an estimated lifetime prevalence of 46% in Stage IV disease, and the detrimental impact of brain metastases on survival.[17] A real-world evidence study estimated a significantly shorter life expectancy for NSCLC patients with brain metastases (25.3 weeks) compared with patients with metastases in the contralateral lung (50.5 weeks), bone (49.4 weeks), adrenal glands (48.7 weeks) and liver (44.9 weeks) ($p<0.01$ for all comparisons).[18]

Available clinical data for selpercatinib evidences its high efficacy in *RET* fusion positive patients with brain metastases: the Summary of Product Characteristics (SmPC) for selpercatinib states that in 23 *RET* fusion-positive NSCLC patients with measurable CNS lesions in the LIBRETTO-001 trial, the overall response rate (ORR) in the evaluable patients was 87%.[19] These data are supported by the subgroup analysis performed in the SAS1 (treatment-naïve NSCLC) trial population of the LIBRETTO-001 trial which found that patients with measurable CNS lesions had a CNS ORR of [redacted].[20]

A17. Subgrouping was also planned for 'race'. In the baseline characteristics table in the company submission (Table 10) four categories are provided: White, Black, Asian and Other. However, in the subgroup analyses in Figure 9 of the company submission only three categories are used: White, Asian and Other. Notwithstanding the expected small numbers (that are observed in other subgroup analyses), please redo the subgroup analysis for 'race' using all four categories.

In the SAS1 population of patients in the LIBRETTO-001 trial, there were only [redacted] patients recorded as 'Black or African American' patients, [redacted] recorded as 'Other' and [redacted] recorded as 'Asian'. Therefore, performing subgroup analyses based on these patient numbers would introduce substantial imprecision and potentially bias given that in a subgroup of [redacted] patients, the estimates might be very far from the subgroup population average. This would occur even if Lilly were to combine the 'Black or African American' subgroup into the 'Other' subgroup; the resulting population size of [redacted] would still be too small to provide robust and reliable subgroup results.

Given that Lilly do not want to exclude these patients from the analysis or combine them with the 'Asian' subgroup, given the known differences for Asian ethnicity, subgroup analyses will not be carried out using all four categories.[4]

Table 6. Ethnicity of patients with *RET* fusion-positive NSCLC lung cancer in LIBRETTO-001

Race, n (%)	SAS1 population ([redacted])
White	[redacted]
Black or African American	[redacted]
American Indian or Alaska Native	[redacted]
American Indian or Other Pacific Islander	[redacted]
Asian	[redacted]
Other	[redacted]
Missing	[redacted]

Abbreviations: SAS: supplementary analysis population.

A18. Any discrepancies between the characteristics of the trial sample and the UK target population may have an impact on the applicability of the trial, provided that discrepant variables are potential outcome modifiers. Given that age, sex, race, ECOG, metastatic disease and CNS metastasis have been identified by the company as potential outcome modifiers (by virtue of being used in pre-planned subgroups), please provide data for the UK target

population for each of these variables (using the categories employed in the baseline characteristics tables [company submission, tables 10 and 11]).

RET fusion-positive NSCLC is a rare condition, with an upper estimate of 2% of all lung cancer cases exhibiting *RET*-fusion.[4] Therefore, there is a lack of data specific to this population of patients in the UK.

Despite this, a Lilly-commissioned survey provided some real-world insights on the characteristics of NSCLC patients from 9 countries, including the UK. Characteristics of the 74 UK patients with treatment-naïve *RET* fusion-positive advanced NSCLC included in the survey are presented in Table 7.[21] Due to the rarity of the disease, data for patients with metastatic disease and CNS metastasis specific to the UK are not available.

The characteristics of patients in the survey are broadly aligned with the baseline characteristics of patients in the SAS1 population of the LIBRETTO-001 trial: median age (64.7 versus [redacted] years, respectively) and the proportion of patients who were not Hispanic or Latino (99% versus [redacted], respectively) were similar. In addition, the majority of patients (70%) in the survey were found to have an ECOG score of 1, which aligned with the patient characteristics reported in LIBRETTO-001 ([redacted]). However, the proportion of males with treatment-naïve advanced NSCLC in the real-world data was higher than reported in LIBRETTO-001 (54% versus [redacted]).[21]

Table 7. Characteristics of patients with treatment-naive advanced NSCLC from Adelphi DSP real-world evidence insights and LIBRETTO-001 trial

Characteristics	NSCLC DSP Wave IV N=74	SAS1 (LIBRETTO-001) [redacted]
Age, years		
Median	64.7	[redacted]
Sex, n (%)		
Male	39 (53)	[redacted]
Female	35 (47)	[redacted]
Race/Ethnicity, n (%)		
Hispanic/Latino	1 (1)	[redacted]
Not Hispanic or Latino	73 (99)	[redacted]
Missing	0 (0)	[redacted]
ECOG score at advanced diagnosis, n (%)		
0	11 (15)	[redacted]
1	52 (70)	[redacted]
2	7 (9)	[redacted]
3	1 (1)	[redacted]
4	3 (4)	[redacted]
Current disease stage, n (%)		
IV or greater	74 (100)	[redacted]
Investigator reported history of metastatic disease, n (%)		
Yes	NR	[redacted]
No	NR	[redacted]
Molecular assay type, n (%)		

NGS with tumour tissue	10 (37)	[redacted]
PCR on tumour	6 (22)	[redacted]
FISH on tumour	15 (56)	[redacted]
NGS on plasma/blood	0 (0)	[redacted]
Nanostring technology	0 (0)	[redacted]

Abbreviations: BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; NR: not reported; SD: standard deviation.
Source: Eli Lilly (data on file). Adelphi DSP real-world evidence insights.[21]

A19. It is pointed out in the company submission that [redacted] of those in the SAS1 dataset had stage IV or greater disease, and that this differs from the proportion of patients in England, where the figure is 46.8%. Given this large discrepancy, a subgroup analysis for cancer stage would appear to be appropriate, even though numbers in the group below stage IV will be small. Please carry out a subgroup analysis for cancer stage.

Disease stage reported in the LIBRETTO-001 trial is based on initial diagnosis and it is unclear whether data from the English National Cancer Registration database are based on initial diagnosis or based on re-assessment. Therefore, these data may not be generalisable.[22] In addition, the eligibility criteria for the LIBRETTO-001 trial stipulated that patients must have locally advanced or metastatic disease.[20] As patients with advanced disease typically have Stage IIIB disease or higher, the proportion of patients with Stage IV disease in the LIBRETTO-001 trial will inherently be higher and therefore will not be generalise to the proportion of patients with Stage IV disease out of the NSCLC population in England (which includes both early and advanced disease patients).[23-25] Therefore, due to this analysis group not being generalisable to England NSCLC statistics, a subgroup analysis is not appropriate.

A20. Priority question: Regarding subsequent therapies:

a) Please provide the distribution of subsequent therapies in LIBRETTO-001.

Of the [redacted] patients in the SAS1 population in the LIBRETTO-001 trial, [redacted] patients went on to receive subsequent therapies, as presented in Appendix A; Table 32 below. To aid interpretation, the proportion of patients receiving each treatment as a proportion of the [redacted] patients who went on to receive subsequent therapies is also presented.

b) Please provide a comparison of this with NHS clinical practice and discuss the implications of any discrepancies.

Subsequent therapy distributions validated by expert clinicians in NHS practice were presented in Table 61 in Section B.3.4.1 of the Company Submission and are reproduced below in Table 8 for ease of reference. Both Table 8 (Appendix A), presenting subsequent therapy data from the SAS1 population of the LIBRETTO trial, and Table 8 below show that no patients received docetaxel or docetaxel plus nintedanib after having received selpercatinib. Additionally, the proportion of patients who received pembrolizumab combination therapy in the LIBRETTO-001 trial was broadly aligned with the subsequent therapy distributions suggested by clinical experts ([redacted] versus 5%, respectively) however, please note that pembrolizumab combination therapy

is not reimbursed at this line of therapy in the UK and therefore was not included as a subsequent therapy treatment option in the scenario analysis provided in the Company submission.

In contrast, in the subsequent therapy distributions from clinical experts, 70% of patients received pemetrexed plus platinum chemotherapy after selpercatinib, whereas [redacted] in the LIBRETTO-001 trial were recorded to receive this combination. Uncertainty surrounding the subsequent treatment distributions utilised in the base case analysis were assessed in a scenario analysis (see Section B.3.10.3 of the Company Submission). As the scenario analysis resulted in minimal impact on the ICERs (see response to Question B21 below), Lilly believe this scenario analysis was sufficient to explore uncertainty surrounding subsequent treatment distributions.

Furthermore, in LIBRETTO-001, a high proportion of patients ([redacted]) were still receiving benefit and continuing on the selpercatinib therapy at the time of the last data cut-off. As such, few patients had discontinued and initiated the new treatment ([redacted]), and thus it is hard to establish a treatment pattern from the data available.

Table 8. Subsequent therapy distributions (expert values) (reproduction of Table 61 from the Company Submission)

Therapy	% Patients After Selpercatinib	% Patients After Chemotherapy	% Patients After Chemotherapy/ Immunotherapy combination therapy
Docetaxel	0	8	10
Docetaxel plus nintedanib	0	32	40
Nivolumab	0	2	2
Pembrolizumab + pemetrexed + platinum chemotherapy[a]	5	0	0
Atezolizumab / pembrolizumab	5	28	13
Pemetrexed + platinum chemotherapy	70	0	0
Best supportive care	20	30	35

[a] Pembrolizumab plus pemetrexed plus platinum-based chemotherapy is not licensed for second-line use in advanced NSCLC patients in the UK. Due to reimbursement restrictions, the following %s are explored in a scenario analysis. After selpercatinib: 80% pemetrexed plus platinum-based chemotherapy, 20% BSC; After chemotherapy: As per table; After chemotherapy/immunotherapy combination: 15% docetaxel, 50% nintedanib plus docetaxel, 35% BSC.
Abbreviations: BSC: best supportive care.

ITC to generate pseudo-comparator arm

A21. Priority question: An ITC using IPD of overall response rate (ORR), progression free survival (PFS) and overall survival (OS) with only pemetrexed and platinum chemotherapy arm was performed. Indeed, an ITC could have

been performed with the other arm of the trial (KEYNOTE-189) from which the IPD for pemetrexed plus platinum chemotherapy was obtained, given that it is also a comparator i.e., pembrolizumab with pemetrexed and platinum chemotherapy.

a) Please justify its choice as opposed to any other comparator in the network or in the scope.

As explained in Section B.2.8.1 of the Company Submission, an ITC using IPD of ORR, PFS and OS with only pemetrexed and platinum chemotherapy was conducted using data from the KEYNOTE-189 trial given that it was the only trial for which the necessary IPD were available. Furthermore, Lilly only had permission and access from the third-party holder to these data from the KEYNOTE-189 trial for this arm of the study, and thus a comparison with pembrolizumab with pemetrexed and platinum chemotherapy, or any other comparator in the network or scope, could not be conducted.

b) Please perform an ITC using IPD of these outcomes with all other comparators in the scope.

As outlined above, performing an ITC using IPD of the outcomes with all other comparators in the scope is not possible given that IPD data for comparators other than pembrolizumab with pemetrexed and platinum chemotherapy from the KEYNOTE-189 trial are not available.

A22. Priority question: Propensity score matching (PSM) was employed in the ITC. Please follow NICE Decision Support Unit (DSU) Technical Support Document (TSD) 17 in assessing which are the best methods for adjusting for confounding and perform at least one other type of adjustment for confounding.

In line with the recommendations provided in NICE TSD17, in addition to PSM, other methods of control arm adjustment were explored, included genetic matching, propensity score weighting (PSW) using a generalised boosted model, and PSW using a logistic regression model. Guidance provided in NICE TSD17 informed the adjustment techiques.[26] The results of the adjustment techniques explored are provided below.

PSM

Propensity score matching uses IPD from one data set to match to another data set. The propensity score for an individual is defined as the probability that the individual receives the treatment, given all the confounding covariates which are being controlled for in the analysis.[27] Specifically, matching aims to replicate randomisation by identifying control individuals who are similar to the treated individuals in one or more characteristics.[26] By matching the outcomes of individuals who differ in the treatment variable, but are otherwise observationally similar, this approach enables estimation of a treatment effect between the interventions under investigation.[26]

Differences in prognostic factors between the selpercatinib arm from LIBRETTO-001 and the placebo plus pemetrexed plus platinum chemotherapy arm from KEYNOTE-189 were adjusted for using propensity score estimated using a multivariable logistic regression approach.[27] The IPD from both trials was used to adjust for between-trial differences in observed baseline characteristics known to have an impact on prognosis (see Table 9 below) and to assess outcomes in a matched population. For completeness, the programming code used for the matching process is provided in Appendix B.

The results of the PSM process are provided below. As expected, and as illustrated in Figure 1 below, the overall balance in patient baseline characteristics between the pemetrexed plus platinum-based chemotherapy and selpercatinib arms improved following PSM.

Table 9. Baseline characteristics of KEYNOTE-189 before and after propensity score matching

Characteristic	SELc (N = [redacted])	Before PSM[a]	After PSM[a]
		PEMc+PLATi (N=[redacted])	PEMc+PLATi (N=[redacted])
Age (mean, years)	[redacted]	[redacted]	[redacted]
ECOG PS = 1, %	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]
Race: Other[b], %	[redacted]	[redacted]	[redacted]
Stage III, %	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]

[a]The analysis followed greedy matching algorithm. [b]Race: other includes non-white, non-Asian and unknown.
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Score; NSCLC: non-small cell lung cancer; PSM: propensity score matching; SEL: selpercatinib.

Figure 1. Standardised differences and variance ratio plot before and after propensity score matching

[redacted]

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process described above to obtain significance tests for the estimated treatment effect, estimate hazard ratios and 95% credible intervals (CrIs) for selpercatinib versus the pseudo-control arm (Table 10).

Table 10: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via PSM

Endpoint	Hazard ratio (95% CrI)	P value
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Abbreviations: CrI: credible interval; OS: overall survival; PFS: progression-free survival; PSM: propensity score matching.

The Kaplan Meier curves for PFS and OS after PSM are presented in Figure 2.

Figure 2: Kaplan-Meier charts for PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following PSM

Solid lines represent the survival data (control arm is matched by prognostic factors: age, the proportion of female patients, the proportion of patients who never smoked, ECOG PS, race, and stage at diagnosis). Shaded portions represent 95% CI.
Abbreviations: PFS: progression free survival; NSCLC: non-small cell lung cancer; OS: overall survival.

Genetic matching

Genetic matching uses a genetic search algorithm to find a set of weights for each covariate such that optimal balance is achieved after matching. For this analysis, models were conducted using R 3.6.0 Linux. For completeness, the programme code used for the matching process is provided in Appendix B.

The results of the genetic matching approach are provided below. As expected and illustrated in Figure 3, the overall balance in patient baseline characteristics between the pemetrexed plus platinum based chemotherapy and selpercatinib arms generally improved following genetic matching.

Table 11. Baseline characteristics of KEYNOTE-189 before and after genetic matching

Characteristic	SELc (N=[redacted])	Before genetic matching	After genetic matching
		PEMc+PLATi (N=[redacted])	PEMc+PLATi (N=[redacted])
Age (mean, years)	[redacted]	[redacted]	[redacted]
ECOG PS = 1, %	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]

Characteristic	SELc (N=[redacted])	Before genetic matching	After genetic matching
		PEMc+PLATi (N=[redacted])	PEMc+PLATi (N=[redacted])
Race: Asian, %	[redacted]	[redacted]	[redacted]
Race: Other[b], %	[redacted]	[redacted]	[redacted]
Stage III, %	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Score; NSCLC: non-small cell lung cancer; PSM: propensity score matching; SEL: selpercatinib.

Figure 3. Standardised differences and variance ratio plot before and after genetic matching

[redacted]

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the genetic matching process described above to obtain significance tests for the estimated treatment effect, estimate hazard ratios and 95% confidence intervals (CIs) for selpercatinib versus the pseudo-control arm (Table 12).

Table 12: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via genetic matching

Endpoint	Hazard ratio (95% CrI)	P value
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Abbreviations: CrI: credible interval; OS: overall survival; PFS: progression-free survival; PSM: propensity score matching.

The Kaplan Meier curves for PFS and OS after genetic matching are presented in Figure 4.

Figure 4: Kaplan-Meier charts for PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following genetic matching

Abbreviations: PFS: progression free survival; NSCLC: non-small cell lung cancer; OS: overall survival.
Note: Solid lines represent the survival data (control arm is matched by prognostic factors: age, the proportion of female patients, the proportion of patients who never smoked, ECOG PS, race, and stage at diagnosis). Shaded portions represent 95% CI.

PSW using a generalised boosted model

PSW using a generalised boosted model was conducted using the "twang" package. For completeness, the programme code used for the weighting process is provided in Appendix B.

The results of the PSW using a generalised boosted model adjustment process are provided below. PSW by generalised boosted model was implemented with two methods of measuring and summarising balance across pre-treatment variables. These were es.mean (mean effect size) and ks.max (maximum of Kolmogorov-Smirnov statistic). They resulted in almost identical balancing results (Table 13). However, it should be highlighted that the effective sample size in the resultant pseudo-control arm (PEMc+PLATi) was smaller than when a matching technique was utilised, making the comparison between arms less powerful.

Table 13: Baseline characteristics of LIBRETTO-001 and KEYNOTE-189 before and after PSW using generalised boosted model

Characteristic	SELc (N=[redacted])	Before PSW	After PSW[a]	
		PEMc+PLATi N = 206	PEMc+PLATi N_{eff} = 50[b]	PEMc+PLATi N_{eff} = 50[c]
Age (mean, years)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS = 1, %	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]	[redacted]
Race: Other, %	[redacted]	[redacted]	[redacted]	[redacted]
Stage III, %	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]	[redacted]

[a]The control arm created by propensity score weighting with generalised boosted model algorithm using two methods of measuring and summarising balance across pre-treatment variables.
[b]es.mean (mean effect size)
[c]ks.max (maximum of Kolmogorov-Smirnov statistic).
Abbreviations: c:continuous; ECOG PS: Eastern Cooperative Oncology Group Performance status; i: induction;

N: sample size; N_{eff}: effective sample size; PEM: pemetrexed; PLAT: platinum; PSW: propensity score weighting; SEL: selpercatinib.

Figure 5. Standardised differences and variance ratio plot before and after propensity score weighing using generalised boosted model

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process described above to obtain significance tests for the estimated treatment effect, estimate hazard ratios and 95% CIs for selpercatinib versus the pseudo-control arm (Table 14).

Table 14: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via PSW using generalised boosted model

Endpoint	Hazard ratio (95% CI)	p-value
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Abbreviations: CI: confidence interval; OS: overall survival; PFS: progression-free survival; PSW: propensity score weighting

The Kaplan-Meier curves for PFS and OS after PSW by generalised boosted model are provided in Figure 6.

Figure 6. Kaplan-Meier charts for PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following PSW using generalised booster model

Solid lines represent the survival data (control arm is matched by prognostic factors: age, the proportion of female patients, the proportion of patients who never smoked, ECOG PS, race, and stage at diagnosis). Shaded portions represent 95% CI.
Abbreviations: CI: confidence interval; NSCLC: non-small cell lung cancer; PFS: progression free survival; OS: overall survival.

PSW using a logistic regression

PSW using a logistic regression model was conducted using the "arm" package which utilises the nearest neighbourhood matching procedure. For completeness, the programme code used for the weighting process is provided in Appendix B.

A comparison of baseline characteristics before and after PSW using logistic regression is presented in Table 15. After applying PSW using logistic regression, baseline characteristics were between the selpercatinib and pemetrexed plus platinum chemotherapy arms were closer aligned (Figure 7). Similar to PSW when using a generalised boosted model, the effective sample size in the resultant pseudo-control arm (PEMc+PLATi) was smaller than when PSM was utilised, making the comparison between arms less powerful.

Table 15: Baseline characteristics of LIBRETTO-001 and KEYNOTE-189 before and after propensity score weighting using logistic regression

Characteristic	SELc (N=[redacted])	Before PSW[a]	After PSW[a]
		PEMc+PLATi N = 206	PEMc+PLATi N_{eff} =31
Age (mean, years)	[redacted]	[redacted]	[redacted]
ECOG PS = 1, %	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]
Race: Other, %	[redacted]	[redacted]	[redacted]
Stage III, %	[redacted]	[redacted]	[redacted]

Characteristic	SELc (N=[redacted])	Before PSW[a]	After PSW[a]
		PEMc+PLATi N = 206	PEMc+PLATi N_{eff} =31
Stage IV, %	[redacted]	[redacted]	[redacted]

[a]The analysis followed greedy match as a matching algorithm.
Abbreviations: c:continuous; ECOG PS: Eastern Cooperative Oncology Group Performance status; i: induction; N: sample size; N_{eff}: effective sample size; PEM: pemetrexed; PLAT: platinum; PSW: propensity score weighting; SEL: selpercatinib.

Figure 7. Standardised differences and variance ratio plot before and after propensity score weighing using logistic regression

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process described above to obtain significance tests for the estimated treatment effect, estimate hazard ratios and 95% CIs for selpercatinib versus the pseudo-control arm (Table 16).

Table 16: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via PSW using logistic regression

Endpoint	Hazard ratio (95% CI)	p-value
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Abbreviations: CI: confidence interval; OS: overall survival; PFS: progression-free survival; PSW: propensity score weighting

The KM curves for PFS and OS after reweighting by PSW using logistic regression are presented in Figure 8.

Figure 8. for PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following PSW using logistic regression

Abbreviations: PFS: progression free survival; NSCLC: non-small cell lung cancer; OS: overall survival.

Conclusion

A clear preference for the selection of an adjustment technique could not be made based on balanced patient characteristics and available estimates alone. PSM was ultimately selected for the adjustment process as the results were associated with the highest external validity; the modelled median PFS and OS were most closely aligned to those observed in KEYNOTE-189 trial for the pemetrexed plus platinum chemotherapy arm (Table 17). In addition, utilisation of a PSM approach resulted in the most conservative estimates of treatment effect: the PSM approach resulted in the highest median PFS and OS estimates for the pemetrexed plus platinum chemotherapy arm (Table 17). This result is externally valid since, as outlined in response to question B.17a) below, patients in the SAS1 population of the LIBRETTO-001 trial were typically younger and healthier than the advanced NSCLC more generally. As a result, the mean age and number of non-smokers for the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial were anticipated to be artificially reduced in the adjustment process, thus resulting in increased mPFS and mOS for this population.

Table 17: Comparison of the modelled landmark survival estimates, mPFS and mOS generated via the different adjustment methods to the observed values from KEYNOTE-189 for the pemetrexed plus platinum chemotherapy arm

Adjustment method	Month 6	Month 12	Month 18	mPFS (months)	Month 6	Month 12	Month 18	mOS (months)
PSM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genetic matching	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSW using generalised booster model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSW using logistic regression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KEYNOTE-189 (observed)	-	-	-	4.9				10.6

Abbreviations: mPFS: median PFS; mOS: median OS; PSM: propensity score matching; PSW: propensity

score weighting.

A23. Priority question: KEYNOTE-189 was used as the source of data for the ITC, although no justification for its choice, as opposed to any other trial, has been provided. Also, the populations were sufficiently different to make propensity sufficient overlap impossible for some variables (e.g., those who "never smoked" comprised [redacted] of the selpercatinib cohort but only 39.1% of the propensity-score-matched pemetrexed and platinum chemotherapy + placebo cohort). Please justify its choice. If it is not demonstrated to be unequivocally better, please perform an ITC using each of those other data sources. Consider using either an individual patient data method according to NICE DSU TSD 17 or a population adjustment method according to NICE DSU TSD 18.

As detailed in response to Question B.17a) below, on average the SAS1 patient population were younger and healthier than patients with NSCLC more broadly, and this is in alignment with what is expected for the *RET*-fusion positive population.[1] For example, whilst there is a paucity of data on the UK population, in Scotland it has been found that roughly 90% of patients with lung cancer are smokers or ex-smokers, compared to [redacted]% of patients in the SAS1 population.[6, 28] As such, it is anticipated that this difference in baseline characteristics would be present and in need of consideration regardless of the trial used for the propensity score matching. However, as noted in the response Question A.21) above, the pemetrexed and platinum chemotherapy arm of the KEYNOTE-189 trial was the only arm with available IPD. For this reason, it was utilised to inform the comparator arm.

An IPD method was chosen over a population adjusted method, such as a matching-adjusted indirect comparison (MAIC) described in NICE DSU 18, because the insufficient data on outcomes would mean that the latter would create greater bias and cause methodological difficulties. In addition, a MAIC would adjust for population 'moments' only, whereas utilisation of an IPD adjustment method allows patients to be matched based on individual baseline characteristics.[29] Owing to the large imbalances in certain baseline characteristics caused by *RET* fusion positive NSCLC patients typically being a younger and healthier demographic than typical lung cancer patients, the use of a population adjusted method would greatly reduce the size of the LIBRETTO-001 dataset (n=[redacted]). This would lead to increased uncertainty in the results of the ITC.

Additionally, this imbalance of key prognostic factors, such as the low percentages of female and Asian patients, is notable in other pemetrexed plus platinum-based chemotherapy trials identified in the NMA, as presented in Table 18. Using summary data would have introduced the additional issue of missing baseline data that may not be reported from publications, such as data that included patients who had never smoked. In addition, there were no other trials which reported any data on patients with specifically *RET* fusion-positive NSCLC.

For these reasons, use of a population adjusted approach was not considered appropriate, and as such, alternative ITC approaches were not conducted.

Table 18. Baseline characteristics

No.	Study, primary author year	Treatment	Median follow-up	Cross-over allowed?	Publication year	Median age (years)	Female (%)	Asian (%)	PD-L1 ≥1% (%)	PD-L1 ≥50% (%)
1	65Plus, Schuette 2017	BEVc+PEMc+PLATi	NR	N	2017	71.5	36.7	NA	NA	NA
		BEVc+PEMc	NR		2017	71.5	36.7	NA	NA	NA
2	BEYOND, Zhou 2015[a]	PACi+PLATi	28.1	Y	2015	56.5	45.0	100	NA	NA
		BEVc+PACi+PLATi	26.9		2015	56.5	45.0	100	NA	NA
3	CameL, Zhou 2021[a]	CAMRc+PEMc+PLATi	11.9	N	2021	60.0	28.5	100	62.0	12.5
		PEMc+PLATi	11.9		2021	60.0	28.5	100	62.0	12.5
4	CheckMate 227, Hellmann 2018	PEMc+PLATi	NR	N	2018	64	33.3	21.05	68.0	34.1
		IPIc+NIVOc	NR		2018	64	33.3	21.05	68.0	34.1
5	CheckMate 9LA, Paz-Ares 2021	PEMi+PLATi+IPIc+NIVOc	13.2	N	2021	65	30	8	60.5	25.5
		PEMc+PLATi	13.2		2021	65	30	8	60.5	25.5
6	CLEAR, Koyama 2018[a]	BEVc+PEMc+PLATi	28.3	N	2018	NA	NA	100	NA	NA
		BEVc+PACi+PLATi	28.3		2018	NA	NA	100	NA	NA
7	Doebele 2015	PEMc+PLATi+RAMc	NR	N	2015	NA	42.12	3.53	NA	NA
		PEMc+PLATi	NR		2015	NA	42.12	3.53	NA	NA
8	EMPOWER-Lung 1, Sezer 2021	CEM	10.8	Y	2021	63.5	14.5	11	NA	NA
		(GEMi or PACi or PEMc)+PLATi	10.9		2021	63.5	14.5	11	NA	NA
9		PEMc+PLATi	27.0	Y	2015	61.0	26.1	NA	NA	NA

No.	Study, primary author year	Treatment	Median follow-up	Cross-over allowed?	Publication year	Median age (years)	Female (%)	Asian (%)	PD-L1 ≥1% (%)	PD-L1 ≥50% (%)
	ERACLE, Galetta 2015	BEVc+PACi+PLATi	27.0		2015	61.0	26.1	NA	NA	NA
10	IMPower 110, Herbst 2020	ATEZc	31.3	N	2020	64.0	29.2	16.2	NA	NA
		PEMc+ PLATi	31.3		2020	65.0	30.3	10.8	NA	NA
11	IMPower130, West 2019	ATEZc+Nab-PACi+PLATi	18.5	Y	2019	64.3	43.0	2.3	NA	19.3
		Nab-PACi+PLATi	19.2		2019	64.3	43.0	2.3	NA	19.3
12	IMPower132, Nishio 2021	PEMc+PLATi	28.4	N	2021	63.5	33.6	23.5	NA	13.1
		ATEZc+PEMc+PLATi	28.4		2021	63.5	33.6	23.5	NA	13.1
13	IMPower132 - China, Lu 2021[a]	ATEZc+PEMc+PLATi	11.7	N	2021	NA	NA	100	NA	NA
		PEMc+PLATi	11.7		2021	NA	NA	100	NA	NA
14	IMPower150, Socinski 2018	BEVc+PACi+PLATi	39.8	N	2018	63	40.1	12.8	NA	23.5
		ATEZc+BEVc+PACi+PLATi	40.0		2018	63	40.1	12.8	NA	23.5
15	Johnson 2004	BEVc+PACi+PLATi	NR	Y	2004	NA	39.4	NA	NA	NA
		PACi+PLATi	NR		2004	NA	39.4	NA	NA	NA
16	Karayama 2016	BEVc+PEMc+PLATi	24.1	Y	2016	65.5	32.8	NA	NA	NA
		BEVi+PEMc+PLATi	24.1		2016	65.5	32.8	NA	NA	NA
17		PEMc+PLATi	49.4	Y	2016	62.9	61.0	8.0	NA	29.9

No.	Study, primary author year	Treatment	Median follow-up	Cross-over allowed?	Publication year	Median age (years)	Female (%)	Asian (%)	PD-L1 ≥1% (%)	PD-L1 ≥50% (%)
	KEYNOTE-021, Langer 2016	PEMc+PEMBROc+PLATi	49.4		2016	62.9	61.0	8.0	NA	29.9
18	KEYNOTE-024, Reck 2016	PEMBROc	59.9	N	2016	64.5	40.3	NA	NA	NA
		(GEMi or PACi or PEMc)+ PLATi	59.9		2016	66.0	37.1	NA	NA	NA
19	KEYNOTE-042, Lopes 2018	PEMc+PLATi	46.9	N	2018	63.0	31.0	NA	NA	100
		PEMBROc	46.9		2018	64.0	30.0	NA	NA	100
20	KEYNOTE-042 - China, Wu 2020[a]	PEMc+PLATi	33.0	N	2020	NA	NA	100	NA	NA
		PEMBROc	33.0		2020	NA	NA	100	NA	NA
21	KEYNOTE-189, Gandhi 2018	PEMc+PLATi	46.3	N	2018	64.5	41.0	NA	NA	32.8
		PEMc+PEMBROc+PLATi	46.3		2018	64.5	41.0	NA	NA	32.8
22	KEYNOTE-189 - Japan, Horinouchi 2021[a]	PEMc+PLATi	18.5	Y	2021	64.8	22.5	100	40	NA
		PEMc+PEMBROc+PLATi	18.5		2021	64.8	22.5	100	40	NA
23	KEYNOTE-598, Boyer 2021	PEMBROc + IPIc	20.6	N	2021	64.0	NA	11.3	NA	100
		PEMBROc	20.6		2021	65.0	NA	10.9	NA	100
24	Lee 2016	PEMc+PLATi	NR	N	2016	NA	NA	NA	NA	NA
		PEMc	NR		2016	NA	NA	NA	NA	NA
25		SELc	9.8	N	2021	60.9	60.0	15.5	NA	NA

No.	Study, primary author year	Treatment	Median follow-up	Cross-over allowed?	Publication year	Median age (years)	Female (%)	Asian (%)	PD-L1 ≥1% (%)	PD-L1 ≥50% (%)
	LIBRETTO-001, Drilon 2020	PEMc+PLATi	9.8		2021	60.9	60.0	15.5	NA	NA
		SELc	9.8		2021	60.9	60.0	15.5	NA	NA
		PEMc+PLATi	9.8		2021	60.9	60.0	15.5	NA	NA
26	LOGIK1201, Fukuda 2019	BEVc+PEMc	NR	N	2019	78.0	42.6	NA	NA	NA
		PEMc	NR		2019	78.0	42.6	NA	NA	NA
27	Niho 2012[a]	PACi+PLATi	NR	Y	2012	60.7	36.0	100	NA	NA
		BEVc+PACi+PLATi	NR		2012	60.7	36.0	100	NA	NA
28	ORIENT-11, Yang 2020[a]	SINTc+PEMc+PLATi	8.9	N	2020	61	23.7	100	67.5	42.3
		PEMc+PLATi	8.9		2020	61.0	23.7	100	67.5	42.3
29	PointBreak, Patel 2013	BEVc+PEMc+PLATi	11.7	Y	2013	NA	NA	NA	NA	NA
		BEVc+PACi+PLATi	11.9		2013	NA	NA	NA	NA	NA
30	PRONOUNCE, Zinner 2015	PEMc+PLATi	NR	N	2015	NA	NA	NA	NA	NA
		BEVc+PACi+PLATi	NR		2015	NA	NA	NA	NA	NA
31	RATIONALE 304, Lu 2021[a]	TISLc+PEMc+PLATi	9.8	N	2021	60.3	26.1	100	NA	32.9
		PEMc+PLATi	9.8		2021	60.3	26.1	100	NA	32.9
32	Sandler 2006	PACi+PLATi	19	N	2006	NA	46.0	NA	NA	NA
		BEVc+PACi+PLATi	19		2006	NA	46.0	NA	NA	NA
33	Socinski 2012	Nab-PACi+PLATi	NR	N	2012	60.0	36.0	23.1	NA	NA
		PACi+PLATi	NR		2012	60.0	36.0	23.1	NA	NA

No.	Study, primary author year	Treatment	Median follow-up	Cross-over allowed?	Publication year	Median age (years)	Female (%)	Asian (%)	PD-L1 ≥1% (%)	PD-L1 ≥50% (%)
34	Spigel 2018	BEVc+PEMc	NR	Y	2018	72.4	42.0	NA	NA	NA
		PEMc	NR		2018	72.4	42.0	NA	NA	NA
		BEVc+PEMc+PLATi	NR		2018	72.4	42.0	NA	NA	NA
35	TASUKI-52, Sugawara 2021[a]	BEVc+PACi+PLATi	13.7	N	2021	66	25.3	100	NA	26.7
		NIVOc+BEVc+PACi+PLATi	13.7		2021	66	25.3	100	NA	26.7

[a]Indicates that the study was conducted in Asian countries.
Abbreviations: ATEZ: atezolizumab; AUC: area under the curve; BEV: bevacizumab; CARB: carboplatin; CAM: camrelizumab; CIS: cisplatin; CTX: platinum doublet chemotherapy; IPI: ipilimumab; ITT: intent to treat; N: no; NIV: nivolumab; NA: not applicable; NBPAC: nab-paclitaxel; PAC: paclitaxel; PBO: placebo; PEM: pemetrexed; Q3W, every 3 weeks; Q4W, every 4 weeks; RAM: ramucirumab; SEL: selpercatinib; TIS: tislelizumab; Y: yes.

A24. Priority question: Please provide a technical report for the ITC and any additional ITCs requested by the EAG, which demonstrates adherence to NICE DSU TSD 17, including completion of the QuEENS checklist. This should address all issues of validation such as:

a) The comparison of different methods of adjustment for confounding

Four different adjustment techniques were assessed for the generation of the pseudo-control arm for the ITC. Descriptions of the methods utilised and the results of each adjustment technique are provided in response Question A22) above.

b) The comparison with an NMA where appropriate

N/A – No NMAs are available which include selpercatinib and therefore a comparison with an NMA was not able to be conducted.

c) The nature of the treatment effect (ATE or ATT)

The treatment effect estimate is ATT (Average Treatment effect on the Treated) in nature, since the LIBRETTO-001 trial did not have randomisation. As outlined NICE DSU TSD 17, the ATE (Average Treatment Effect) calculates the expected effect of the treatment if individuals in the population under consideration were randomly allocated to treatment; this is the effect that would be identified by a randomised controlled trial. Broadly speaking, this parameter is the most difficult to identify given that it requires more demanding assumptions for identification than alternative treatment effects like ATT. In the submitted approach, available IPD for the pemetrexed plus platinum-based chemotherapy arm of the KEYNOTE-189 study are matched/weighted in order to make them comparable to the population available in LIBRETTO-001.

d) Appropriateness of model specification such as proportional hazards

The appropriateness of the proportional hazard assumption was checked for the selpercatinib versus pemetrexed plus platinum-based chemotherapy arm using ‘R function cox.zph: Test the Proportional Hazards Assumption of a Cox Regression’. The assessment showed that the p-value for the OS curves was [redacted] and for PFS curves [redacted], indicating no significant departure from the proportionality of hazards.

e) Appropriateness of the assumption of selection on variables with a full description of the means by which prognostic and treatment effect modifiers were identified

A separate SLR (SLR2) was conducted to inform the appropriate selection of variables which were prognostic to be included in the analysis. Full details of the search strategy and results of SLR2 are presented in Appendix C. The final selection of variables included in the analysis was done in consultation with clinical experts.

f) Assessment of overlap and balance post-adjustment

The impact of the alternative adjustment techniques on the baseline characteristics of the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial is provided in response to question A.22) above.

g) Assessment balance of covariates

An assessment of the balance of covariates for the four alternative adjustment techniques assessed is provided in response to question A.22) above.

h) The details of any matching such as whether with replacement

The two matching methods utilised to adjust for confounding (PSM and genetic matching) were both done without replacement. For completeness, the programming language utilised for the different adjustment techniques assessed is provided in Appendix B.

i) The effect on sample size and variance of any method of adjustment

The effect on sample size and variance of the four methods of adjustment assessed for suitability for utilisation in the ITC is provided in response to A.22 above.

A25. In addition to the 142 patients excluded from the KEYNOTE-189 cohort, 5 patients were removed from the SAS1 dataset (n=69) to facilitate propensity matching. The reasons were ECOG PS = 2 ([redacted]) and missing stage data ([redacted]). Removal of participants is a necessary part of propensity-matching. However, in this case it appears that 4/5 excluded from the SAS1 dataset were those with the poorest ECOG score, which could lead to a spurious benefit to be observed for the study drug.

a) Please state whether the decisions on exclusions in the SAS1 database were made pre-hoc.

Lilly can confirm that the decision on patient eligibility was made *pre-hoc*, before the matching/weighting approaches were attempted.

b) If so, please explain the decision-making process underlying the pre-hoc exclusion strategy.

The reason for this pre-hoc decision on exclusion from the SAS1 database being made was that the KEYNOTE-189 study had an inclusion criterion to enrol only patients with an ECOG performance score of 0 or 1. Therefore, it would not be possible to find patients from the KEYNOTE-189 trial who matched the [redacted] patients with an ECOG score of 2 in the SAS-1 population of the LIBRETTO-001 trial.

SLR

A26. Priority question: In section B.2.1 of the company submission, it states that only "*first-line to progression studies*" were included. The justification for this in Appendix D section D1.1 is that selpercatinib is administered *"…until progression (or unacceptable toxicity)".*

a) Please explain why the method in which selpercatinib is administered should determine the inclusion of studies of comparator treatments.

As it is anticipated that selpercatinib will be administered 'until progression or until acceptable toxicity occurs' in UK clinical practice, the first line to progression treatment setting aligns more closely with the decision problem.[30] In all studies categorised as "first line", the maximum number of treatment cycles were fixed in the study design and the number of treatment-cycles allowed in these studies varied but were limited to 6 cycles at most (see Appendix D). The "First line to progression" category included regimens where one or more treatments in the combination were allowed to be administered until progression and study regimens with fixed number of cycles and study regimens which allowed maintenance/continuation beyond "induction" were not considered comparable, even with the same drugs included. Accordingly, only studies reporting 'first line to progression' treatments were deemed relevant for inclusion in the NMA and were reported in Appendix D of the Company Submission. Lilly acknowledges that treatments that are administered for a fixed number of cycles or with fixed stopping rules are relevant to clinical practice in the NHS, such as pembrolizumab which is a key component of the pembrolizumab combination therapy comparator with a 2-year stopping rule. However, these treatment rules are a consequence of NICE guidance rather than the trial design themselves. As such, it was expected that the first line to progression studies would capture all relevant trials for the decision problem.

For completeness, all first-line studies that were included in SLRs 1–4, and which therefore could have been included in the NMA but were excluded based on the wording presented above, are provided in Appendix D. The only treatment included in these trials that could be relevant to the decision problem is pemetrexed plus platinum-based chemotherapy. However, pemetrexed is used as "maintenance" and given until progression in clinical practice in the platinum-based chemotherapy combination regimen (NG122)[30] while the regimen included in these studies are given as an "induction" for a fixed number of cycles, therefore, none of the studies report on treatments relevant to the decision problem. Furthermore, the most appropriate trial for the comparison was concluded to be the control arm (pemetrexed plus platinum-based chemotherapy) of the KEYNOTE-189 trial, explained in in response to question A23). In KEYNOTE-189 the number of cycles of pemetrexed was not fixed but allowed to be administered until progression. As such, limiting the NMA to include only first line to progression studies will not have excluded any data relevant to the current appraisal.

b) If any comparator treatments are administered for a fixed number of cycles or for a fixed time period, then please include studies of those treatments when this is the case.

Please see response to question A26a), limiting the NMA to include only first line to progression studies will not have excluded any data relevant to the current appraisal.

c) Please verify that the criterion 'until progression' is equivalent to 'until progression or unacceptable toxicity'.

Lilly can confirm that the criterion 'until progression' is equivalent to 'until progression or unacceptable toxicity.

A27. The SLR protocol (Table 25 in Appendix D section D1.2) only allows the inclusion of RCTs for primary research papers. However, the company statement in the text of the appendices suggests that a post-hoc amendment was made to the protocol, to permit additional inclusion of, '*single-arm trials reporting data from patients with RET fusion-positive NSCLC and data from RCTs in the wider non-squamous NSCLC population'*. This amendment should have been reflected in the wording of the final protocol, for greater transparency.

a) Please explain when this amendment was made to the protocol, and whether it was a post-hoc change.

At the time that the original SLR was conducted in July 2018, the comparator trials published in *RET* fusion-positive NSCLC were not of particular interest. For the update of the SLR conducted in July/August 2020, the protocol was amended in order to support selpercatinib HTA appraisals to include single arm trials for selpercatinib and pralsetinib. This reflected that both treatments were expected to have market access based on single arm clinical trials and that no RCT data were expected to be published. As such, this amendment was implemented in order that potentially relevant comparator information not be missed in the systematic review. Since the update to the SLR in July/August 2020, the single arm trials for specific RET inhibitors have been eligible for inclusion in the SLR.

b) This change led to the inclusion into the SLR of LIBRETTO-001 (a single arm trial) as well as LIBRETTO-321 (which was also a single arm trial). Despite LIBRETTO-321 being included in the SLR, please explain why LIBRETTO-321 was not included in the clinical efficacy review, even though it contained an eligible subgroup (treatment naïve RET fusion-positive NSCLC).

At the time that data extraction was ongoing for the clinical SLR, no results from the LIBRETTO-321 trial were available. As such, no data were extracted, but the first trial disclosure were captured in SLR5 from a congress abstract. A full manuscript was subsequently published after the SLR5 search date.[31]

The LIBRETTO-321 trial was conducted in China and recruited patients from China only. As noted in response to Question A17) above, there are known differences for the Asian race in NSCLC.[4] As such, the generalisability a fully Asian cohort of patients to UK clinical practice is limited. In addition, at the time of the latest data cut off (March 2021), 47 patients diagnosed with *RET*-fusion positive NSCLC had been recruited, of which only 11 had their *RET* status confirmed. Of those with a confirmed *RET* status, only 8 patients were treatment naïve. Therefore, this change led to the exclusion of relatively immature data from only 8 patients, the results of which are anticipated to have limited applicability to the UK.

Based on this, Lilly maintain that the amendment made was appropriate and did not lead to the exclusion of any relevant data.

NMA

A28. Priority question: The company used a pseudo-comparison with pemetrexed plus platinum chemotherapy for the NMA.

a) Please justify why this treatment was used as opposed to any other for the NMA.

As outlined in response to A21 above, and as mentioned in Section B.2.8.1 of the Company Submission, KEYNOTE-189 was the only trial to provide IPD and the pemetrexed plus platinum chemotherapy was used as a pseudo-comparison because Lilly only had permission to use IPD from this arm of the KEYNOTE-189 trial.

b) Please discuss any differences between the results of the treatment effect estimated using the NMA and the results of ITCs as requested in A12.

As discussed in response to Question A23, imbalances in baseline characteristics caused by RET-fusion positive patients typically being younger and healthier than NSCLC patients as a whole means that population-adjusted methods such as a MAIC would reduce the available sample size and introduce uncertainty and potentially bias to the analyses. As such, an IPD method has been selected and the use of a population adjusted approach is not presented.

c) Please conduct sensitivity analyses using ITCs with any of the other comparators in the scope as requested in A12 to produce a ‘pseudo-comparator’ for connection to the NMA network.

As noted above, the lack of available IPD mean it is not possible to conduct an ITC with comparators other than pemetrexed plus platinum chemotherapy.

A29. Priority question: The complete results of the NMA for all comparators in the scope or the care pathway for RET fusion positive advanced NSCLC in NICE guideline 122 are not presented in the company submission nor the appendices. On the other hand, the networks presented in the company

submission and the accompanying tables of included studies in Appendix D include studies for comparators that are neither in the scope or the care pathway for RET fusion positive advanced NSCLC in NICE guideline 122, e.g. bevacizumab with pembrolizumab and platinum chemotherapy. Therefore, for all outcomes for which a NMA was conducted (and for any further NMAs requested in A19), and for all/only the comparators in the scope or the care pathway for RET fusion positive advanced NSCLC in NICE guideline 122, please provide the following:

a) A network diagram for each outcome (ORR, OS and PFS)

The NMA which analysed OS, PFS and ORR to provide relative treatment effect estimates of comparative efficacy between selpercatinib and comparators was conducted from a Global perspective to inform reimbursement activities across various geographies. As such, additional comparators that are not relevant to the UK setting were included. Given their lack of relevance to the current submission (see response to Question A9 for further detail), an updated network diagram for each outcome that includes these other treatment options has not been provided.

b) A set of tables (like Tables 29 to 37) showing the study characteristics and outcomes

As discussed in response to Part a) of this question, this information is not provided given that Lilly do not consider these treatment options to represent relevant comparators in the current appraisal.

c) A grid for each outcome detailing the NMA treatment effect estimates (HRs and ORs) for all permutations of treatment comparisons involved in the network, as well as a ranking of all treatments involved in the network.

As discussed in response to Part a) of this question, this information is not provided given that Lilly do not consider these treatment options to represent relevant comparators in the current appraisal.

Section B: Clarification on cost-effectiveness data

Model structure

B1. Priority question: The NICE DSU TSD 19 recommends the use of state transition models (STMs) alongside partitioned survival models (PSMs) to

verify the plausibility of PSM extrapolations and to explore key clinical uncertainties in the extrapolation period.

a) Please justify the use of a partitioned survival approach given the issues highlighted in NICE DSU TSD 19, particularly regarding the extrapolation of PFS and OS while assuming structural independence between these endpoints.

Lilly acknowledge that strong justification of the chosen model structure is paramount and as such both the partitioned survival model (PSM) and state transition model (STM; of which Markov is a common type) approaches have been compared and contrasted, considering previous NICE technology appraisals, in the guidance from TSD19 and published literature.[1, 29, 32-34]

Lilly acknowledge that a PSM approach assumes that the modelled survival endpoints are structurally independent and that this may represent a limitation of the selected approach. In addition, the PSM approach may over- or under-estimate long-term outcomes if the hazard rate changes over time such that the hazard rate calculated from the observed period does not accurately reflect the expected hazard ratio in the extrapolated period. However, estimates from a PSM and Markov models typically converge as the data mature and prior NICE appraisals of oncology treatments indicates that the choice of a PSM or STM approach typically has a limited impact. As such, the risk of long-term over- or under-estimation of PFS outcomes with a PSM, and thus the potential benefit of a STM versus a PSM in this regard, is limited.

Another possible advantage of choosing a STM approach, such as a Markov model, would be to include additional health states either to capture the disease course in more detail, or to allow for more complex modelling of subsequent therapies. However, it is not clear that additional health states over and above the 3-state 'progression-free, post-progression, dead' PSM structure are required to capture the disease course of advanced NSCLC, or that subsequent therapies need to be captured in greater detail. In addition, an assessment of HTAs in SCLC found that both the PSM and Markov model approaches produced fairly accurate replications of observed survival outcomes, but the PSM approach produced marginally more accurate replications.[24]

The preference for a PSM approach is reflected in prior NSCLC NICE submissions, where there is clear precedent for a PSM, and no strong criticisms from EAGs have been received on this approach.[7, 32-34] This is expected as PSMs make for intuitively appealing models that replicate within-study data with relative ease given that there is direct correspondence between reported time-to-event endpoints (PFS and OS) and the survival functions. In addition, STM require strong assumptions such as a constant probability of death in the progressed disease health state. These assumptions can lead to an increased risk that the model will not accurately represent outcomes within the period covered by the clinical evidence.[35] Further to this, due to the sparsity of data in this indication, use of an STM would require the transition probabilities between states to be informed by assumptions. In comparison, data collected during the LIBRETTO-001 trial can be directly implemented in a PSM, reducing the need for strong structural assumptions.

Overall, owing to the arguments presented above and the validity of the outcomes provided by a PSM, Lilly maintain that the PSM approach presented in the Company Submission is the most appropriate approach for this submission.

b) Please use state transition modelling to assist in verifying the plausibility of the PSM extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11).

As discussed in answer to Part a) of this question, Lilly do not consider that recommendation 11 of NICE DSU TSD 19, which discusses the use of a STM to verify the plausibility of an PSM or address uncertainties in the extrapolation period, to be relevant to this appraisal given that the PSM provides a robust reflection of clinical reality, is in alignment with prior NICE appraisals in NSCLC, and makes best use of the available data in a rare indication. As such, a STM has not been presented.

Intervention and comparators

B2. Priority question: Pembrolizumab monotherapy, atezolizumab, atezolizumab plus bevacizumab, carboplatin and paclitaxel and chemotherapy were not included as comparators, although they were all included in the NICE scope.

a) Please provide an updated economic model and scenario analyses including all relevant comparators as per the NICE scope. Please provide the results of a fully incremental analysis (and updated economic model used for this analysis) with all comparators listed in the scope as comparators modelled separately.

As outlined in response to Question A9, Lilly do not consider pembrolizumab monotherapy, atezolizumab, atezolizumab plus bevacizumab, carboplatin and paclitaxel and chemotherapy to be relevant comparators to selpercatinib, as supported by UK clinical expert feedback and the pralsetinib appraisal.[34] Therefore an updated model and scenario analyses including these comparators has not been provided.

b) Please provide an updated model and scenario analysis corresponding to each of the additional ITC and NMA analyses requested in Section A, including an ITC based on IPD for pembrolizumab with pemetrexed and platinum chemotherapy from KEYNOTE-189.

As outlined in response to Question A24 on the availability of IPD, and as Lilly do not consider that these treatments represent relevant comparators in this appraisal, an updated model and scenario analyses corresponding to each of the additional ITC and NMA analyses including these comparators have not been provided.

Population

B3. The baseline characteristics for the model population (provided in company submission Table 38) included age, sex and weight, and were based on the baseline characteristics of patients who received selpercatinib in the LIBRETTO-001 trial. It was stated by the company, that based on clinical expert feedback, the baseline characteristics of the LIBRETTO-001 trial were considered to be representative of patients in UK clinical practice.

a) Please demonstrate this by providing data on age, sex and weight for the UK target population.

RET fusion-positive NSCLC is a rare condition, with an upper estimate of 2% of all lung cancer cases exhibiting *RET*-fusion.[4] Therefore, there is a lack of data specific to this population of patients in the UK.

However, the Lilly-commissioned survey discussed in response to Question A18 does provide some real-world insights on the characteristics of NSCLC patients from 9 countries, including the UK. Data on age and sex for patients from the UK with treatment-naïve *RET* fusion-positive advanced NSCLC in the survey are presented in Table 19. These characteristics are broadly aligned between patients enrolled in the survey and the baseline characteristics of patients in the SAS1 population of the LIBRETTO-001 trial. Body weight data were not available from the survey results and cannot be provided.

Table 19. Characteristics of patients with treatment-naive advanced NSCLC from Adelphi DSP real-world evidence insights and LIBRETTO-001 trial

Characteristics	NSCLC DSP Wave IV (N=74)	SAS1 (LIBRETTO-001) (N=[redacted])
Age, years		
Median	64.7	[redacted]
Sex, n (%)		
Male	39 (53)	[redacted]
Female	35 (47)	[redacted]

Abbreviations: DSP: disease specific programme; NSCLC: non-small cell lung cancer.
Source: Eli Lilly (data on file). Adelphi DSP real-world evidence insights.[21]

b) For any discrepancies between the characteristics of the LIBRETTO-001 trial sample and the UK target population, please provide an updated economic model and scenario analysis using the characteristics of the UK target population.

With respect to the median age of patients, there were minimal discrepancies identified between the SAS1 population of the LIBRETTO-001 trial and patients with *RET* fusion-positive NSCLC in the UK enrolled to the survey. Minor discrepancies in terms of the sex distribution are observed between the two cohorts, but this is not expected to be impactful, and expert clinicians consulted

by Lilly did not comment that the LIBRETTO-001 data diverged notably from their expectations of *RET* fusion-positive patients in UK clinical practice.

Due to the lack of available body weight data in the survey, it is not possible to compare body weight between the LIBRETTO-001 trial patients and patients in UK clinical practice. However, during clinical validation with the expert oncologists, median body weight data for the SAS1 population were presented to the oncologists who were then asked whether the data were generalisable to UK clinical practice. The oncologists concluded that the weight data available from the SAS1 population of the LIBRETTO-001 trial aligned well with their expectations for the weight of *RET* fusion-positive patients in UK clinical practice.[36] Therefore, it is likely that the body weight of patients in the LIBRETTO-001 trial is representative of patients with *RET* fusion-positive NSCLC in the UK.

Given the anticipated generalisibility between the LIBRETTO-001 trial population and the expected population in clinical practice, an updated economic model and scenario analysis has not been provided.

Effectiveness

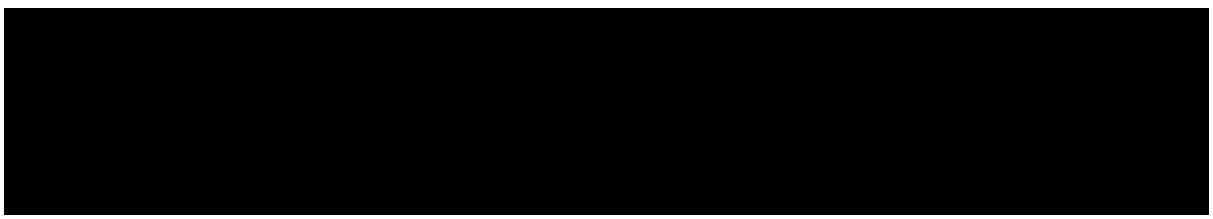
B4. Priority question: The estimation of parametric survival models seems only partly consistent with reported guidance from NICE DSU TSD 14 and 21 on (flexible methods for) survival analyses. Please provide the following for OS, PFS and time to treatment discontinuation (TTD), separately for the intervention and comparators:

As LIBRETTO-001 was a non-comparative, single-arm trial the requested figures are not available for TTD and therefore cannot be provided. The available information for OS and PFS is presented below.

a) Tables with the numbers of patients at risk, per 3 months.

The tables containing the numbers of patients at risk, per 3 months, for OS and PFS are provided in Figure 9 and Figure 10, respectively.

Figure 9. The numbers of SAS1 patients at risk of OS at three-month intervals in the LIBRETTO-001 trial



Abbreviations: OS: overall survival; SAS1: Supplemental Analysis Set 1.

Figure 10. The numbers of SAS1 patients at risk of PFS at three-month intervals in the LIBRETTO-001 trial

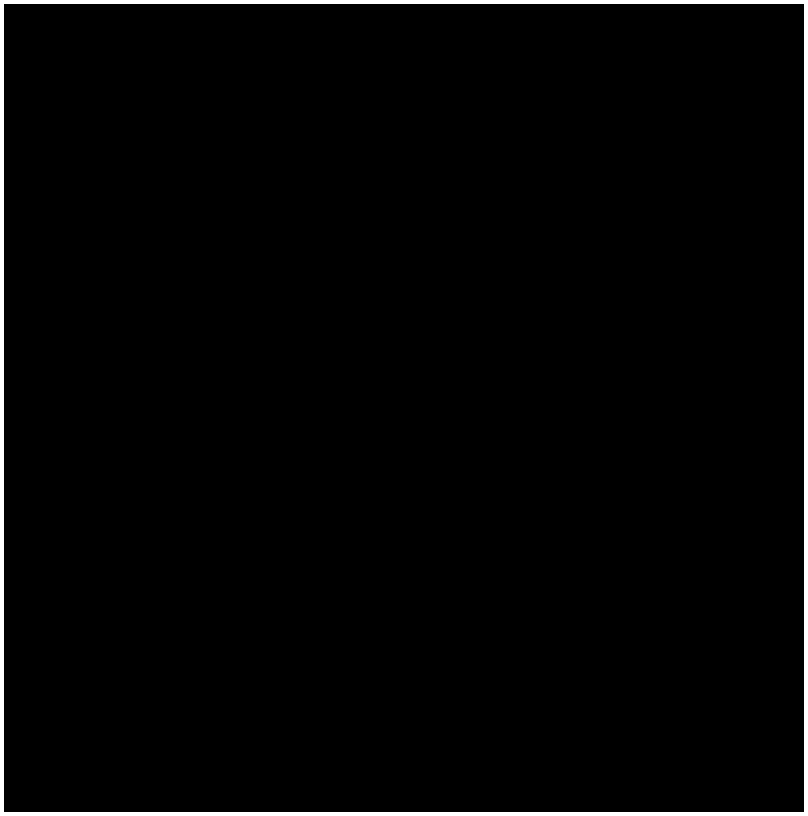
Abbreviations: PFS: progression free survival; SAS1: Supplemental Analysis Set 1.

b) To examine the proportional hazard assumption:

i. Plot the scaled Schoenfeld residuals versus time (all survival curves)

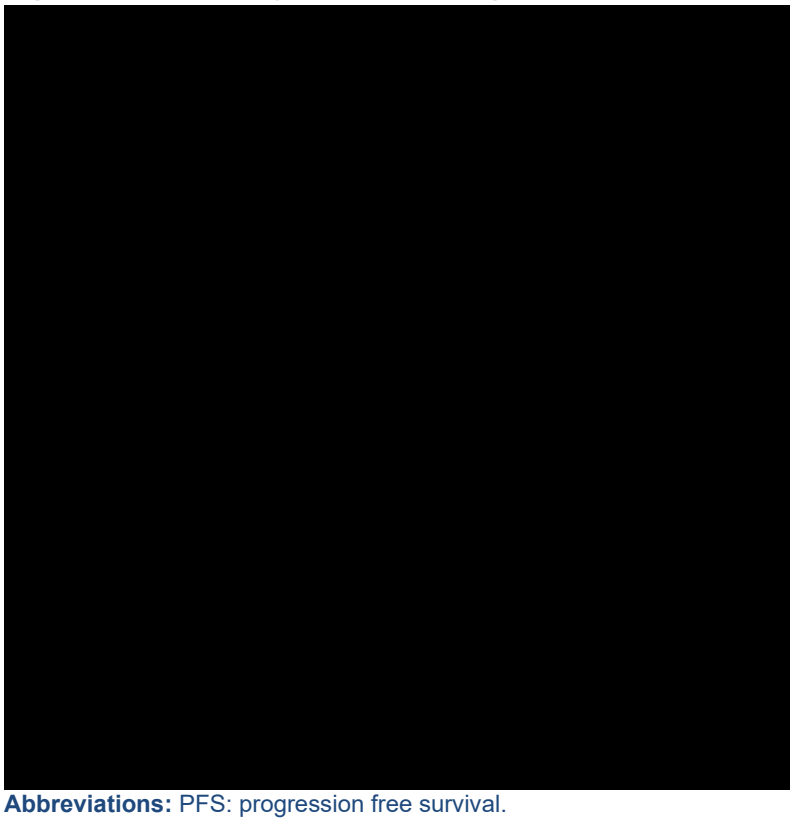
The scaled Schoenfeld residuals versus time (for all survival curves) for OS and PFS are provided in Figure 11 and Figure 12, respectively.

Figure 11. Propensity score matching Schoenfeld plot of OS



Abbreviations: OS: overall survival.

Figure 12. Propensity score matching Schonefeld plot of PFS patients



Abbreviations: PFS: progression free survival.

ii. Plot the log cumulative hazard versus log time

The propensity score matching log-log plots for OS and PFS, are presented in Figure 13 and Figure 14, respectively.

Figure 13. Propensity score matching log-log plot of OS

Abbreviations: OS: overall survival; RET: rearranged during transfection.

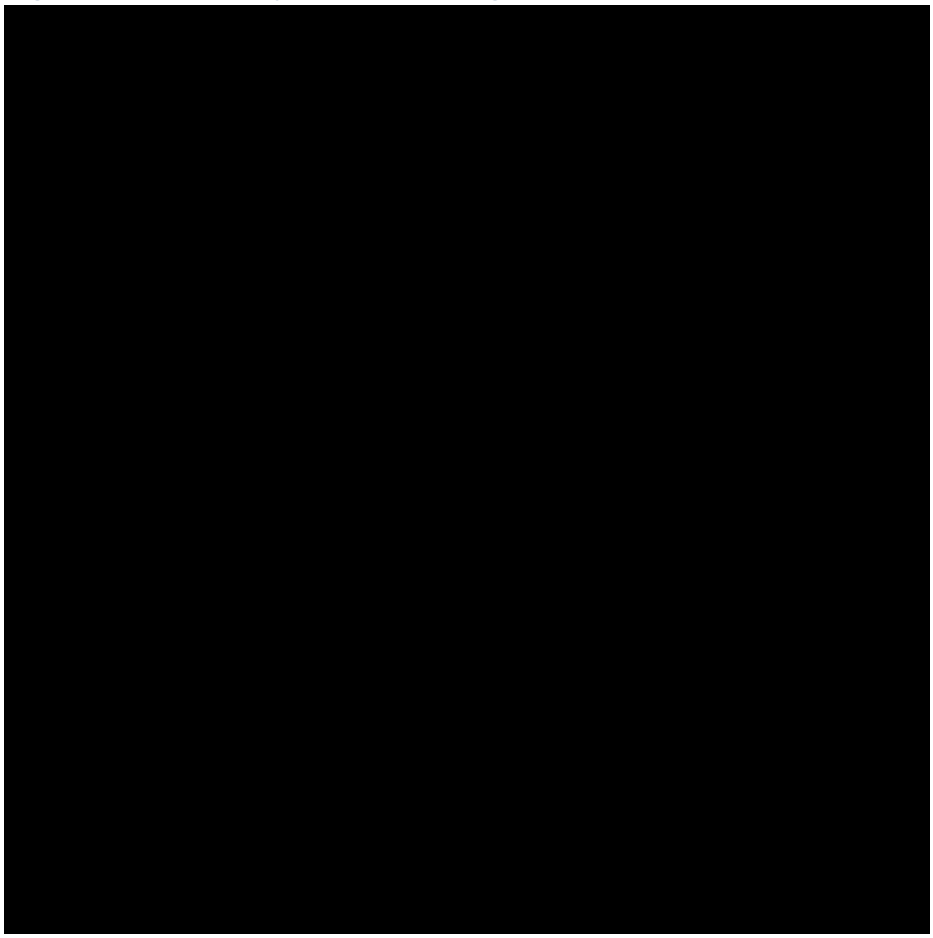
Figure 14. Propensity score matching log-log plot of PFS

Abbreviations: PFS: progression free survival; RET: rearranged during transfection

c) To examine the heuristics of the hazard function over time, plot the smoothed hazards over time

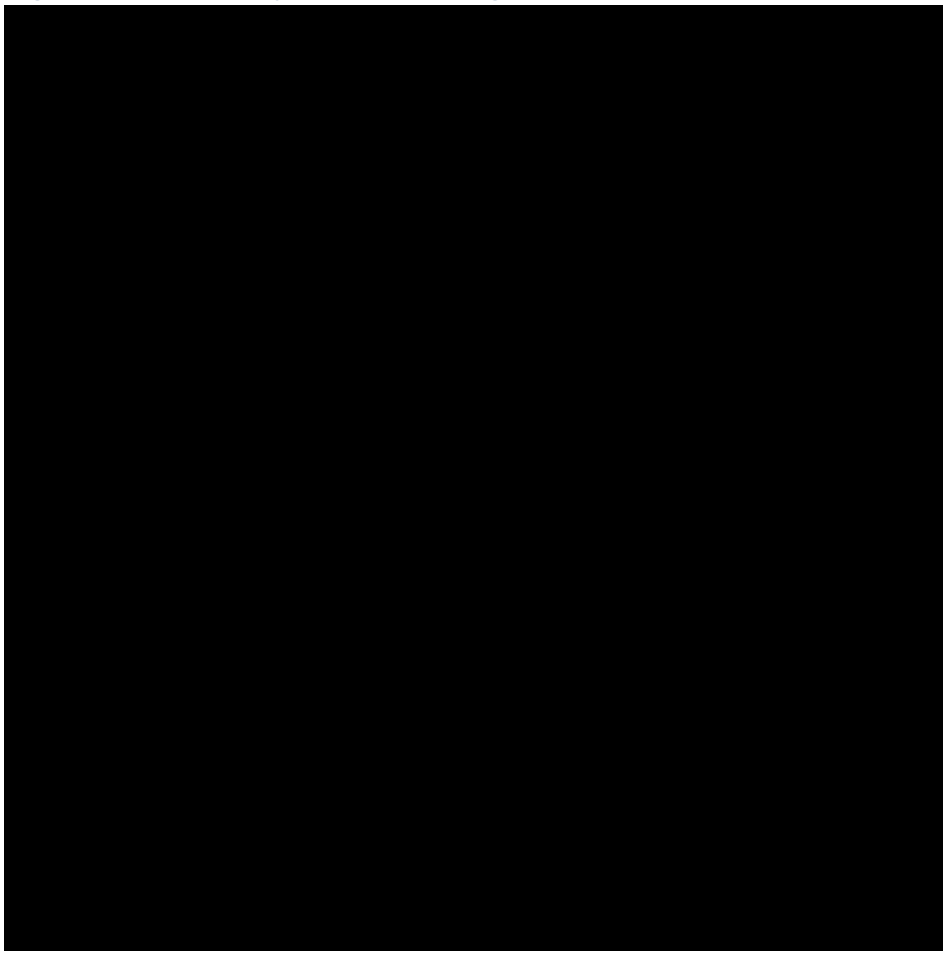
The propensity score matching smoothed hazard rate plots for OS and PFS, are presented in Figure 15 and Figure 16, respectively.

Figure 15. Propensity score matching smoothed hazard rate plot of OS



Abbreviations: OS: overall survival.

Figure 16. Propensity score matching smoothed hazard rate plot of PFS



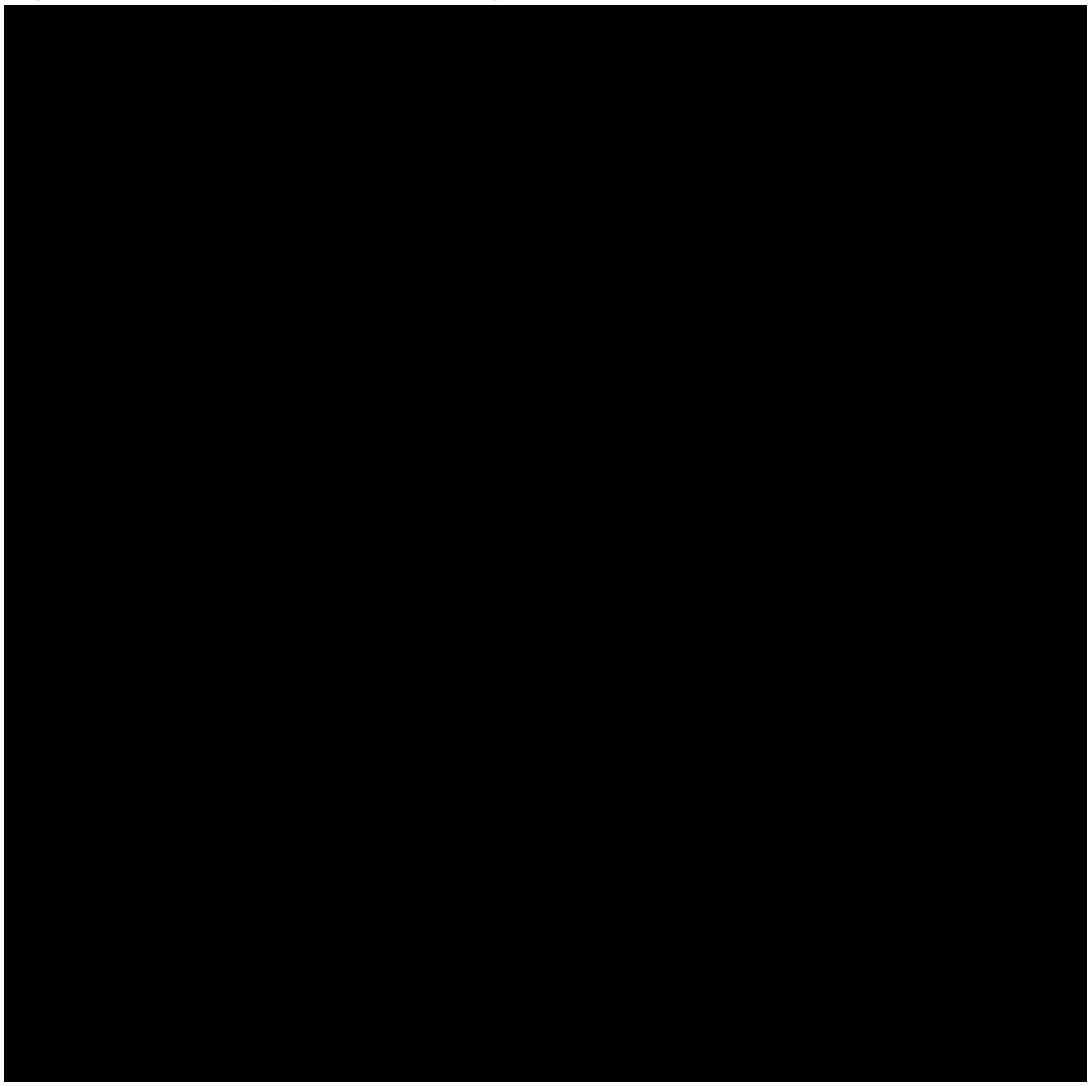
Abbreviations: PFS: progression free survival.

d) To examine diagnostics of parametric survival models (using the observed data):

    i. Plot the cumulative hazard versus time

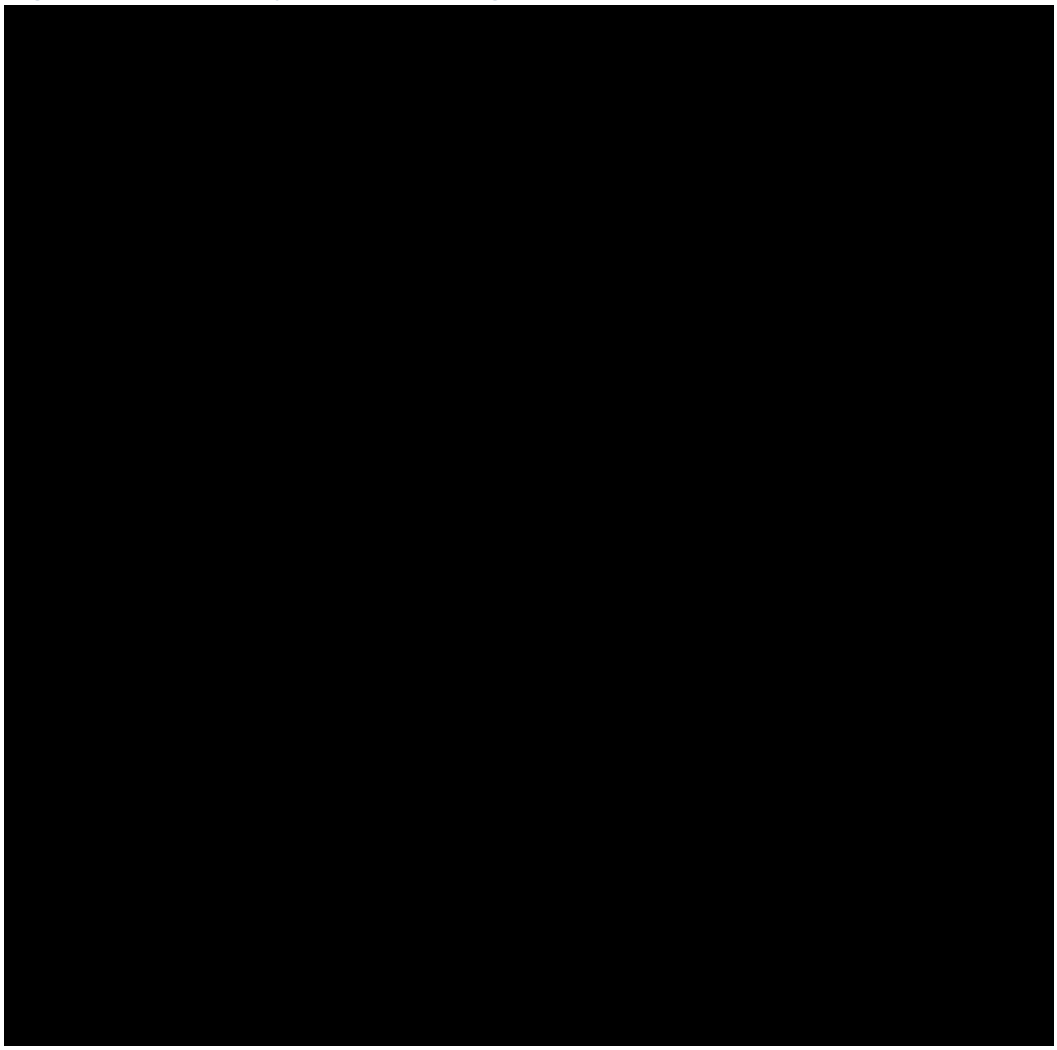
The propensity score matching Nelson-Aalen hazard rates plots for OS and PFS, are presented in Figure 17 and Figure 18, respectively.

Figure 17. Propensity score matching Nelson-Aalen hazard rates plot of OS



Abbreviations: OS: overall survival.

Figure 18. Propensity score matching Nelson-Aalen hazard rates plot of PFS



Abbreviations: PFS: progression free survival.

ii. Plot the log smoothed hazard versus time

Lilly understand that these requested figures are the same as the cumulative hazard versus time figures provided above in Part ci) of this question. As such, please refer to the response to Part ci) above.

iii. Plot the standard normal quartiles versus log time

Lilly apologise that the figures presenting standard normal quartiles versus log time are not available to be presented here.

iv. Plot the log survival odds versus log time

Lilly apologise that the figures presenting survival versus log time are not available to be presented here.

e) To examine the validity of the extrapolation beyond the data, please provide supporting evidence that the extrapolations are consistent with relevant

external data and/or expert opinion. In case of expert opinion, please provide a full description of the methods and results for the conducted expert consultation.

As outlined in Section B.3.2 of the Company Submission, the choice of survival distribution selected in the base case analysis was informed by feedback received from expert oncologists practicing in NHS clinical practice and alignment with external data. For transparency, the slide deck utilised during the clinical validation meetings as well as the minutes from the meeting have been provided alongside the clarification question responses.[11, 37]

PFS

The Gompertz distribution was selected as the base case survival curve for PFS for all treatment arms. As outlined in Table 41 of the Company Submission and summarised in Table 20 below, landmark estimates generated when using the Gompertz distribution aligned well with those provided by the clinical experts.

In addition, one of the clinical experts advised that survival estimates for selpercatinib in *RET* fusion-positive patients could be deemed comparable to those of *ALK*-positive patients treated with targeted therapies.[9] Two such therapies are brigantinib and alectinib, which were assessed in the ALTA-1L and ALEX trials, respectively.[12, 38] Median PFS for these two therapies was found to be 24.02 and 34.8 months, respectively. The median PFS estimated for selpercatinib with the Gompertz curve was [redacted] months which compares to more conservative benchmark estimates from trials in other targeted therapies. Further to the above, the Gompertz distribution is associated with a short tail, and feedback from clinical experts obtained in the pre-treated submission for selpercatinib (TA760)[7] was that targeted therapies are not anticipated to be associated with a long tail.

The Gompertz distribution also provided good external validity for the pemetrexed plus platinum-based chemotherapy and pembrolizumab combination arms, with the modelled median PFS for each generally aligning to the results of the KEYNOTE-189 trial (4.9 and 9.0 months compared to [redacted] and [redacted] for the modelled arms).[39]

Table 20. External validation of base case survival analysis for PFS

	Median PFS (months)		
	Selpercatinib	**Pemetrexed plus platinum chemotherapy**	**Pembrolizumab combination therapy**
Base case: Gompertz	[redacted]	[redacted]	[redacted]
Expert opinion	21	6–11	10–11
KEYNOTE-189	N/A	4.9	9.0
ALTA-1L	24.02	N/A	N/A
ALEX	34.8	N/A	N/A

Abbreviations: N/A: not applicable; PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on file. Clinical validation meeting minutes.[9] KEYNOTE-189.[39] ALTA-1. ALEX.[40]

OS

The spline knot 1 distribution was selected as the base case survival curve for OS for all treatment arms.

The landmark estimates generated when using the spline knot 1 model were generally consistent with those provided by the expert oncologists for selpercatinib and comparators as provide in Table 44 of the Company Submission and summarised in Table 21 below. The predicted long-term landmark rates were within the range given by the clinical experts (1–10%). In addition, the modelled median OS for selpercatinib was consistent with a real-world evidence study (Tan *et al.* 2020)[41] evaluating OS in a population of *RET* fusion-positive NSCLC patients treated with a selective *RET* tyrosine kinase inhibitor ([redacted] vs 49.3 months, respectively). The estimates for selpercatinib with the spline knot 1 function also aligned well with those for the *ALK-1* inhibitor alectinib (48.2 months).[40]Furthermore, the spline knot 1 model provided good external validity versus trial data, with the modelled median OS for each comparator aligning approximately to the results of the KEYNOTE-189 trial (22.0 and 10.6 months for the pembrolizumab combination and pemetrexed plus platinum-based chemotherapy arms, respectively).[39]

Table 21. External validation of base case survival analysis for OS

	Median OS (mts)		
	Selpercatinib	**Pemetrexed plus platinum chemotherapy**	**Pembrolizumab combination therapy**
Base case: Spline knot 1	[redacted]	[redacted]	[redacted]
Expert opinion	50–72	12–24	12–24
ALK-1	48.2	N/A	N/A
Tan *et al.* (2020)	48.33	N/A	N/A
KEYNOTE-189	N/A	10.6	22.0

Abbreviations: mts: months; N/A: not applicable; OS: overall survival.
Source: Eli Lilly and Company Ltd. Data on file. Clinical validation meeting minutes.[9] KEYNOTE-189.[39] Tan et al. (2020).[41] ALK-1.[38, 40] ALEX.[38, 40]

TTD

An exponential curve was selected for the base case survival analysis for time to treatment discontinuation (TTD) for selpercatinib. An exponential curve was deemed externally valid as it provided landmark estimates which lay above the PFS landmark estimates. Feedback received from expert oncologists noted that a proportion of patients stay on treatment post-progression for a short period of time.[9]

f) Please justify the selection of the approaches to estimate and extrapolate OS, PFS, and TTD, considering the responses to the preceding questions as well as the "Survival Model Selection Process Algorithm" provided in NICE DSU TSD 14.

A detailed stepwise explanation of the Company base models for PFS, OS and TTD are provided in Section B.3.2 of the Company Submission. Lilly acknowledge that the detail of internal validity assessments were lacking in the original submission. However, a greater emphasis was placed on external validity of the extrapolations given the relative immaturity of PFS and OS data for

selpercatinib, as described in response to B4e). As per NICE DSU TSD 14: '*If there is a large amount of clinical trial survival data over a long time period it may be reasonable to assume that a parametric model that fits the data well will also extrapolate the trial data well. Also, when survival data are relatively complete the extrapolated portion may contribute little to the overall mean area under the curve and in this case the log-cumulative hazard plots and AIC/BIC test results may be of particular use*.'[42] However, in this case, the observed survival data required substantial extrapolation and therefore the clinical validity of the extrapolation was used to guide selection of the most appropriate model. Approximately [redacted] months of PFS and [redacted] months of OS were reliant upon extrapolated data where <1% are alive. In contrast, TTD data were relatively mature and as such, goodness-of-fit statistics were considered a more valid method to guide model choice. For completeness, a description of the methodological approach and assessment of internal validity tests, as recommend in the NICE DSU TSD 14, has been provided below.

Methodology

Proportional hazards assumption

The PH assumption can be investigated using both qualitative assessment and quantitative assessment, as listed below:

1. **Log-cumulative hazard plots:** Log-cumulative hazard plots can be constructed to illustrate the hazards observed in the trial. A hazard plot of the log(cumulative hazard) against log(time) was used to assess proportionality of hazards over time and identify potential important changing points, with parallel curves of the different treatment arms indicating that the PH assumption was not violated. It is important to note that assessing parallelism is rather subjective, and non-crossing of the hazards does not conclude that the PH assumption is met. Additional graphical and statistical tests are needed to assess this assumption.

2. **Schoenfeld residuals test:** Testing for time dependency of the hazard ratio is equivalent to testing for a non-zero slope in a generalised linear regression of the scaled Schoenfeld residuals over time. A non-zero slope is an indication of a violation of the PH assumption. If the log(HR) does not fall within the 95% confidence interval (CI) bands, it could be a strong indicator for violation of proportionality between the two curves.

Survival extrapolation approaches

In accordance with NICE DSU TSD 14, the range of parametric distributions fitted to the selpercatinib, and comparators arms are described below:

PFS

As outlined in Section B.3.2 of the Company Submission, the following parametric functions were explored as part of the survival analysis for PFS:

- Unstratified (with treatment as an indicator variable) exponential, Weibull, Gompertz, lognormal, loglogistic, generalised gamma and gamma
- Stratified Weibull, Gompertz, lognormal, loglogistic, generalised gamma and gamma
- Unstratified and stratified spline models, with one, two and three knots

OS

The approach to parametric survival curve selection mirrored that of PFS; the recommendations of NICE Decision Support Unit (DSU) TSD 14 were followed.[42] Stratified spline knot models were not considered for OS as the models did not coverage. The following set of curves were explored for selpercatinib and the reference arm (and consequently the pembrolizumab combination therapy arm):

- Unstratified (with treatment as an indicator variable) exponential, Weibull, Gompertz, lognormal, loglogistic, generalised gamma and gamma
- Stratified Weibull, Gompertz, lognormal, loglogistic, generalised gamma and gamma
- Unstratified spline models, with one, two and three knots

TTD

The following parametric functions were explored as part of the survival analysis for TTD:

- Unstratified exponential, Weibull, Gompertz, lognormal, loglogistic, generalised gamma and gamma
- Unstratified spline models, with one, two and three knots

It is acknowledged that spline models with more intermediate knots such two or three knot can sometimes be considered clinically implausible and associated with the risk of "overfitting" the data. However, given the relatively immaturity of the selpercatinib data for PFS and OS, and the lack of relevant external data for validation, these options were included to assess the clinical plausibility of their extrapolations.

Model selection

As outlined in Section B.3.2 of the Company Submission, selection of the appropriate extrapolation model was based on the statistical fit of the models to the trial data, informed by AIC and BIC statistics, as well as visual inspection of the survival curves and more importantly, the external validity of the extrapolations. Additional considerations as per the recommendations provided in NICE DSU TSD 14 are provided below.

Assessment of proportional hazards and smoothed hazards for PFS and OS

Please note that an assessment of the proportional hazards and smoothed hazards was only possible for the selpercatinib and pemetrexed plus platinum-based chemotherapy arms of the model as adjusted KM data was applied directly and used to estimate the extrapolation. For the pembrolizumab combination arm, HRs were applied to the pemetrexed plus platinum-based chemotherapy arm.

The PH assumption between the selpercatinib and pemetrexed plus platinum-based chemotherapy arms was tested. The log-log plot in Figure 13 and Figure 14, for PFS and OS respectively shows the treatment arms appear to move in parallel for the entire period. This is consistent with the Schoenfeld residuals visualisation in Figure 11 and Figure 12 for PFS and OS respectively in which no clear time trend can be observed, suggesting no violation of the PH assumption. This gives some confidence that the original PH models for PFS (Gompertz) and OS (spline knot 1) were appropriate. Since the PH assumption for pembrolizumab combination therapy was accepted by applying HRs to the pemetrexed plus platinum-based chemotherapy arm, the models for PFS and OS are also acceptable for this comparator treatment arm.

Additionally, a visual assessment of the smoothed hazard curves for selpercatinib and pemetrexed plus platinum-based chemotherapy for OS shows there may be some non-monotonicity with the hazard function fluctuating for selpercatinib up until month [redacted]. This suggests that more flexible models may be appropriate and validates the choice of the spline knot 1 model for OS. Further information relating to the selection of the spline knot 1 model for OS is provided in response to Question B5.

g) The company states that "If visual assessment and clinical plausibility was not met, then different models were explored for each arm, to ensure that clinically valid estimations were made". Please state for which parametric models this was done.

For a complete list of the parametric models explored as part of the survival analysis for PFS, OS and TTD, please see response to Part f) of Question B5 above, under the '*Survival extrapolation approaches'* subheading.

Scenario analyses

Following exploration using the various curve choices, the base case curves were selected as outlined in Section B.3.2 of the Company Submission. However, in order to explore the impact of extrapolation curve choice, several scenario analyses were conducted and presented in Section B.3.10.3 of the Company Submission in which alternative curve choices were implemented. These included:

- Exponential, Weibull, stratified Weibull and spline knot 1 for PFS
- Separate curves for comparator arms: Spline knot 3 and exponential for OS
- Spline knot 3 and exponential for OS applied separately to the pemetrexed plus platinum-based chemotherapy and pembrolizumab combination comparator arms only (spline knot 1 for selpercatinib arm)
- Gompertz, Weibull and gamma for TTD

The results of these scenario analyses demonstrated that the base case ICERs were moderately sensitive to variations in the survival functions used to extrapolate OS, but none resulted in a substantial change to the base case ICERs.

h) In company submission, page 113, paragraph 3 it states that the proportional hazard assumption did not hold for PFS and that therefore treatment-specific curves were explored in the scenario analysis. Please explain why, when the proportional hazard assumption does not hold, the company preferred modelling parametric curves together instead of in a treatment specific manner.

As stated in Section B.3.2.2 of the Company Submission, with the overall uncertainty from unanchored indirect treatment comparisons (ITCs) and most trials meeting the proportional hazard (PH) assumptions, it was deemed acceptable to apply the PH assumption in the base case.

i) The EAG could not identify scenario analyses with separate comparator curves for PFS. Please conduct scenario analyses with separate comparator curves for PFS, including the following scenario, based on difference between median survival time estimated by survival curves and by expert opinion: Log-normal for selpercatinib, Weibull for the comparator arm. For scenario analyses of your choosing please justify your choice of survival curves appropriately.

Lilly thank the EAG for highlighting this discrepancy. The omitted scenario analysis is provided below along with the requested scenario in this question. Although the internal validity assessments support the original base case of a joint PH model applied to selpercatinib and the comparator arms, Lilly acknowledge the original trial informing the HR estimates for pembrolizumab combination therapy applied in the model showed non-proportionality. Therefore, separate curves were explored in a scenario analysis.

The scenario analyses preferred by Lilly are based on the clinical plausibility of the extrapolation compared to the clinical expert landmark estimates given the relatively immaturity of PFS and OS data (see response to Question B5f). Based on expert opinion, there are number of distributions that produce more optimistic survival estimates for the comparator arms. As such, Exponential and spline knot 1 are explored in scenario analyses. It should be noted that applying the lognormal extrapolation to the selpercatinib arm may produce a clinically implausible tail with almost [redacted]% and [redacted]% still progression-free at 10- and 20-years, respectively, and the Weibull may underestimate PFS for the comparator arms. Therefore, Lilly caution that this scenario is unlikely to reflect clinical reality and therefore is not suitable for decision making..

Table 24: Survival curves landmark PFS estimates compared to clinical expert values for comparator arms

Survival curves	Selpercatinib					Pemetrexed plus platinum chemotherapy					Pembrolizumab combination therapy[a]				
	Median PFS (mts)	Survival (%)				Median PFS (mts)	Survival (%)				Median PFS (mts)	Survival (%)			
		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year
Exponential	[redacted]	37.08	19.14	3.66	0.13	[redacted]	0.81	0.03	0.00	0.00	[redacted]	8.26	1.57	0.02	0.00
Weibull	[redacted]	33.03	13.29	1.05	0.00	[redacted]	0.17	0.00	0.00	0.00	[redacted]	3.72	0.25	0.00	0.00
Lognormal	[redacted]	34.35	19.80	7.30	1.98	[redacted]	4.33	1.54	0.28	0.04	[redacted]	N/A	N/A	N/A	N/A
Gompertz	[redacted]	35.20	15.15	0.95	0.00	[redacted]	0.51	0.01	0.00	0.00	[redacted]	6.50	0.72	0.00	0.00
Spline knot 1	[redacted]	38.57	21.86	5.68	0.45	[redacted]	0.90	0.05	0.00	0.00	[redacted]	8.70	2.03	0.06	0.00
Spline knot 2	[redacted]	39.69	23.86	7.44	0.90	[redacted]	1.11	0.09	0.00	0.00	[redacted]	9.72	2.69	0.14	0.00
Spline knot 3	[redacted]	42.14	28.96	13.26	3.71	[redacted]	1.39	0.22	0.00	0.00	[redacted]	10.89	4.16	0.56	0.02
Expert opinion	21	30-35	15	3-5	1-5	6-11	15	<5-5	0-<1	0-<1	10-11	15	<5-5	0-<1	0-<1

[a] Estimates were not obtained for parametric survival functions for pembrolizumab combination therapy where the proportional hazards assumption does not apply (stratified and unstratified generalised gamma, lognormal and loglogistic).
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; mts: months; N/A: not applicable; NR: not reported; PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on file. Clinical validation meeting minutes.[9]

Table 25: Scenario analyses – Separate curve choices for intervention and comparator arms, PFS

Scenario		Selpercatinib vs pembrolizumab + pemetrexed + platinum chemotherapy			Selpercatinib vs pemetrexed + platinum chemotherapy		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	***5,264***	[redacted]	[redacted]	***35,883***
1	Intervention: Gompertz Comparator: Spline Knot 1	[redacted]	[redacted]	4,378	[redacted]	[redacted]	35,789
2	Intervention: Gompertz Comparator: Exponential	[redacted]	[redacted]	4,038	[redacted]	[redacted]	35,789
3	Intervention: Lognormal Comparator: Weibull	[redacted]	[redacted]	7,825	[redacted]	[redacted]	35,667

Exponential TTD curves applied in these scenario analyses as per Company base case.
Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; LY: life years; NHB: net health benefit; NSCLC: non-small cell lung cancer; QALYs: quality-adjusted life years.

B5. Priority question: A spline knot 1 model is used to model OS for selpercatinib and the comparators. According to the NICE DSU TSD 21, flexible models are required when hazard functions are observed or expected to have complex shapes in the longer-term. The EAG did not find any explanation on whether the hazard functions are expected to have complex shapes.

a) Please justify why standard parametric survival models were not considered sufficient to estimate PFS and OS for selpercatinib and the comparators.

Selection of an appropriate survival function for selpercatinib and comparators for PFS and OS was based on the internal and external validity of the survival functions. As extrapolations for pembrolizumab combination therapy were generated via application of a HR to the reference arm, it was deemed statistically appropriate to explore functions to which the proportional hazards assumption applies, specifically, the exponential, Gompertz and Weibull functions. In addition, in the interest of maximising clinical plausibility of the extrapolations in the *RET* fusion-positive population, exploration of the fit of a further range of survival functions was also conducted, specifically, accelerated failure time (AFT) models (gamma, lognormal and loglogistic functions), stratified functions and spline models. As such, both standard and non-standard parametric models were assessed in terms of their internal and external validity to find the most suitable distribution.

The fit of these functions to the Kaplan-Meier data across treatment arms for selpercatinib and relevant comparators was explored. As described in Section B.3.2 of the Company Submission, as the AIC/BIC statistics provided similar fits to the observed Kaplan Meier data for both the

selpercatinib and reference arm for all survival functions, it was not possible to select an optimal curve choice based on internal validity. As such, selection of the appropriate survival function for OS and PFS relied heavily on the external validity of the curve. Owing to the paucity of data in this field, external validity was informed by clinical experts who treat *RET* fusion positive patients in UK clinical practice and real-world evidence in other targeted treatments in NSCLC.

PFS

Ultimately a standard parametric model, the Gompertz distribution, was selected to model PFS for both selpercatinib and comparators owing to its high external validity. Detailed justification of the selection of a Gompertz distribution for PFS are provided in Section B.3.2.2 of the Company Submission and are summarised in response to Question B.4e) above.

OS

Owing to the small number of OS events in LIBRETTO-001, the external validity of the survival function was particularly important when selecting the most appropriate function for OS. Ultimately, a spline knot-1 model, which is not a standard parametric model, was selected to model OS for selpercatinib and comparators. Similarly to PFS, the curve choice was guided by its high external validity. The landmark estimates generated for the selpercatinib and comparator arms when using the spline knot 1 model were broadly consistent with those provided by the expert oncologists for selpercatinib and generally aligned better than those produced when using standard parametric models.

However, the exponential distribution produced similarly consistent values to the spline knot-1 model. The spline knot-1 model was ultimately chosen over the exponential distribution for selpercatinib as it aligned closer with real-world evidence in other targeted treatments in NSCLC.[40, 41] Areal-world evidence study by Tan *et al.* 2020[41] evaluating OS in a population of *RET* fusion-positive NSCLC patients treated with a selective *RET* tyrosine kinase inhibitor found median OS to be 49.3 months when compared to a modelled median OS of [redacted] and [redacted] produced by the spline knot-1 and exponential distribution, respectively. The estimates for selpercatinib with the spline knot 1 function also aligned closer with those for the *ALK-1* inhibitor alectinib (48.2 months) than when using the exponential distrubtion.[40]

In addition to the alignment with clinical expert opinion (see Table 22 below), the spline knot 1 model also provided good external validity versus available trial data for the comparator arms, with the modelled median OS for each comparator aligning approximately to the results of the KEYNOTE-189 trial (22.0 and 10.6 months for the pembrolizumab combination and pemetrexed plus platinum-based chemotherapy arms, respectively).[39]

The exponential distribution was explored in scenario analysis for OS for both selpercatinib and comparators arms, the results of which are presented in Section B.3.10.3 of the Company Submission. Switching to an exponential distribution resulted in minimal impact on the base case ICERs for both pemetrexed and platinum chemotherapy and pembrolizumab combination therapy ([redacted] and [redacted], respectively).

Table 22: Survival curves landmark OS estimates compared to clinical expert values

Survival curves	Selpercatinib					Pemetrexed plus platinum chemotherapy					Pembrolizumab combination therapy				
	Median OS (mts)	Survival (%)				Median OS (mts)	Survival (%)				Median OS (mts)	Survival (%)			
		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year
Exponential	[redacted]	61.97	45.05	20.29	4.12	[redacted]	13.36	3.49	0.12	0.00	[redacted]	29.33	12.95	1.68	0.03
Weibull	[redacted]	58.67	36.16	8.69	0.28	[redacted]	6.38	0.53	0.00	0.00	[redacted]	18.70	4.08	0.05	0.00
Lognormal	[redacted]	59.87	43.07	22.65	9.24	[redacted]	18.16	9.11	2.81	0.65	[redacted]	N/A	N/A	N/A	N/A
Loglogistic	[redacted]	58.90	40.01	19.11	7.72	[redacted]	15.57	7.90	2.95	1.07	[redacted]	N/A	N/A	N/A	N/A
Gompertz	[redacted]	57.55	26.92	0.08	0.00	[redacted]	6.12	0.13	0.00	0.00	[redacted]	18.23	1.76	0.00	0.00
Gamma	[redacted]	58.50	36.44	10.00	0.63	[redacted]	7.47	0.97	0.00	0.00	[redacted]	N/A	N/A	N/A	N/A
Spline Knot 1	[redacted]	60.68	41.88	15.74	1.97	[redacted]	9.46	1.64	0.02	0.00	[redacted]	23.77	8.18	0.49	0.00
Clinical Experts	50-72	60	45-50	20	1-10	12 to 24	25-40	6-17	<1-5	0-<1	12 to 24	25-40	6-17	<1-5	0-<1

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; mts: months; N/A: not applicable; NR: not reported; PFS: progression free survival.
Source: Eli Lilly and Company Ltd. Data on file. Clinical validation meeting minutes.[9]

b) For the spline knot 1 model used for the company base case, please clarify how many patients were at risk (per treatment) after the specified knot location.

As there was no clear change in the KM shape, the default option of flexsurvspline R function was used to estimate the spline knot models. The knots were then chosen as equally spaced quantiles of the log uncensored survival times. At the median with one knot, this corresponded to 7.4 months on the linear scale. At this time, more than 50% of patients were still at risk in the OS arms for pemetrexed plus platinum-based chemotherapy (~[redacted] patients) and selpercatinib (~[redacted] patients). It should be noted that research conducted by PC Lambert *et al.* (2017) and Jackson C *et al.* (2017) found that the determination of knot location(s) does not appear critical for good fit.[43, 44] In addition, given the immaturity of the OS data for which the spline knot 1 is applied in the Company base case, the knot location is less relevant here.

c) Please justify, also based on the responses to the previous question, the use of the spline knot 1 model, i.e., why specifically one knot, and why specifically the hazards scale, were used?

The log hazard scale is commonly used in extrapolation methods. As stated previously, OS data for selpercatinib is relatively immature with only ~[redacted] observed events. For this reason, clinical plausibility of the extrapolations was given greater weight and was a prominent feature for model choice for the OS functions applied in the Company base case. An assessment of the smoothed hazard plots presented in response to Pard d) of Question B4 shows that the hazard function fluctuates, increasing and decreasing until month 27, showing non-monotonicity. In this case, models such as the Weibull or Gompertz, which assume monotonically increasing or decreasing hazards, and the exponential, which assumes a constant hazard rate, are expected to fit less well to the observed data. In contrast, accelerated failure time models such as the lognormal and loglogistic which do not assume a monotonic hazard function over time and are able to reflect turning points in the underlying hazard function may fit better to the observed data.[44] This is reflected in the AIC/BIC scores for OS presented in Table 43 of the Company Submission. Spline-based models use natural, cubic, piecewise polynomials to smooth between sections of a transformation of the baseline survivor function. Royston and Parmar (2002) provide a detailed description of these models and suggest the use of these flexible parameterisations to better reflect the “behaviour” of the hazard rate over time.[45] The changing hazards scales shown in the smoothed hazards (Figure 15) plots also support the case for more flexible spline-based functions and supports the Company base case choice for OS. However, given the relative immaturity of the survival data for selpercatinib, Lilly caution the conclusions drawn from any of the internal validity assessments shown in response to Question B4.

d) When extrapolating based on spline-based models, linearity is assumed (on a transformed scale of the survival function), which may result in implausible projections. Please justify that the linearity assumption is plausible for extrapolating (technically beyond the last placed knot).

As noted in the response to clarification question B.4b) above, the knot occurs at 7.4 months for selpercatinib. Lilly acknowledge that a linearity assumption for the reminder of the extrapolation

may be a strong assumption give the immaturity of the OS data. However, given the paucity of long-term OS data in the population relevant to this submission, the selection of an appropriate survival distribution for OS was informed by landmark estimates provided by clinical experts and alignment with external data for other targeted therapies in NSCLC (see response to Question B.4e above).

In order to account for the uncertainty around the survival distribution used in the base case analysis, other survival models were explored in several scenario analyses presented in the Company Submission, which included both standard and non-standard parametric models. The results of these analyses are presented in Section B.3.10.3 of the Company Submission. The base case results were found to be robust to variations in the survival distribution utilised.

e) Please provide an updated economic model and scenario analysis (deterministic and probabilistic) selecting the most appropriate standard parametric survival curve for the modelling of OS based on NICE DSU TSD 14.

The economic model submitted alongside the Company Submission includes the functionality to select standard parametric distribution options as well as more flexible survival functions. Furthermore, as discussed in response to Question B4g, scenario analyses were provided in Section B.3.10.3 of the Company Submission which explored the impact of implementing the standard parametric survival curves which were deemed to provide the clinically valid predictions compared to the values provided by the expert oncologists. These scenario analyses did not result in a substantial change to the base case ICER, providing confidence that curve choices are not key model drivers.

As such, an updated economic model and further scenario analyses implementing standard parametric survival curves for modelling OS are not provided.

B6. Priority question: In the company's base case analyses, selpercatinib TTD and PFS curves cross.

a) Please justify the plausibility of crossing of these lines, especially considering that consulted experts stated that patients usually remain on treatment until they had received 2 more scans.

Lilly acknowledge that the TTD and PFS curves for the selpercatinib arm cross during the extrapolation period. However, Lilly wish to emphasise that for the base case analysis, the selected curve for TTD lay above PFS for the majority of the extrapolation, which aligns with expert oncologist opinion that a proportion of patients stay on treatment post-progression for a short period of time. In contrast, the majority of other curve choices for TTD lay below the PFS extrapolation, indicating that most patients discontinue treatment before progression, which does not retain clinical plausibility. While the log-normal and log-logistic TTD curve options did lie above the PFS curve, they were deemed to overestimate TTD and were associated with a worse statistical fit than the base case option. As such, Lilly maintain that the PFS and TTD curve choices presented in the Company Submission are suitable.

b) The company states that using the exponential curve for TTD for selpercatinib was due to its clinical plausibility (as it lies above PFS landmark estimates). However, in the company base case analysis, the company models TTD using the exponential curve with a median duration of 23.93 months and models PFS using the Gompertz curve with a median duration of [redacted]. Please clarify this potential inconsistency with the statement above, and/or elaborate on what is meant by "the exponential curve for TTD lying above the PFS landmark estimates".

Extrapolation of trial-based TTD data is a standard approach utilised in technology appraisals in order to obtain treatment duration for an intervention of interest.[7] In line with the methodology taken for PFS and OS detailed in response to question B.4e) above, a range of standard parametric distributions were explored to extrapolate time to treatment discontinuation (TTD) data from the LIBRETTO-001 trial. As noted in response to Part a) of this question, feedback received from expert oncologists consulted as part of the appraisal process noted that patients who progress are often kept on treatment until they have received a further two scans, delivered approximately 3 months apart.[9] As such, the selection of curves which model the TTD curve lying above the PFS curve retains a high external validity. On the other hand, the maturity of the TTD data obtained from the LIBRETO-001 trial means that the goodness of fit of the curve to the observed data provides strong internal validity. As such, both aspects were considered in the selection of the base case TTD extrapolation.

As outlined in Section B.3.2.4 of the Company Submission, consideration of the AIC and BIC statistics resulted in the exponential distribution being selected as the base case curve for TTD for selpercatinib as the best statistically fitting curve option. The Kaplan Meier data for PFS and TTD presented in Figure 19 below show the TTD and PFS data were similar at earlier timepoints and crossing, and the high statistical fit of the selected curves led to the extrapolated data reflecting the slight observed trend towards TTD lying above PFS. Lilly acknowledge the minor inconsistency in the statement that the exponential curve lies above the PFS landmark estimates while the median PFS lies above median TTD, but wish to emphasise that for the base case analysis, the selected curve for TTD lay above PFS for the majority of the extrapolation, which aligns with feedback received from expert oncologists and makes best use of the relatively mature data available.

Figure 19: Selpercatinib PFS and TTD Kaplan Meier curves from the LIBRETTO-001 trial

Abbreviations: KM: Kaplan Meier; PFS: progression free survival; TTD: time to treatment discontinuation.

c) Please provide an updated economic model and scenario analysis where the median difference between TTD and PFS is closer to 6 months (as estimated by experts) or [redacted] (as measured in LIBRETTO-01).

The results of a scenario analysis in which a mean time from progression to treatment discontinuation of [redacted] days as informed by the LIBRETTO-001 trial are presented in Table 23.

Table 23. Scenario analysis – Applying mean time from progression to treatment discontinuation (LIBRETTO-001)

Scenario		Selpercatinib vs pembrolizumab + pemetrexed + platinum chemotherapy			Selpercatinib vs pemetrexed + platinum chemotherapy		
		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	***5,264***	[redacted]	[redacted]	***35,883***
1	TTD: Mean time from progression to discontinuation	[redacted]	[redacted]	7,185	[redacted]	[redacted]	37,415

Footnotes: Company base curves applied for PFS (Gompertz) and OS (Spline Knot 1).
Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; NSCLC: non-small cell lung cancer; QALYs: quality-adjusted life years.

B7. In Table 40 and Table 43 of the company submission, model fit statistics for the intervention and comparator are presented together.

a) Please justify presenting these statistics together instead of individually.

Stratified functions were used rather than separate functions for each treatment arm to allow comparison of model fit statistics (Akaike information criterion and Bayesian information criterion) with those for the unstratified functions. The unstratified model evaluates a treatment effect as a relative effect of the two treatment arms. This adds a 'treatment' parameter to the model and assumes proportional hazards. The alternative is either to have two separate models for each arm, or to fit a stratified model, but neither of these approaches would evaluate a treatment effect and proportional hazards is not assumed or relied upon.

The stratified model fits each arm separately, using the same distribution form but different parameters. In addition, the stratified model permits some information to be shared across arms, representing another advantage in the case of small sample sizes such as in the RET-fusion positive population of interest to this appraisal. Therefore, only one model was fitted (with stratification by treatment) and thus only one set of the fit statistics was generated and presented.

b) Please present model fit statistics for selpercatinib and the reference arm separately.

Separate model fit statistics for selpercatinib and the reference arm are not available and therefore have not been provided.

c) Please comment on how the individually fitted statistics change the choice of survival curves.

N/A – No individually fitted statistics for selpercatinib and the reference arm are available. Individually fitted models were not attempted given small sample sizes and potential unreliability of the fit.

d) Please present a scenario analyses with survival curves based on question c. of this clarification question.

N/A – Please see the responses to questions B.7a) and b) above.

B9. The EAG understands that company uses a propensity score matching analysis to compare selpercatinib with pemetrexed + platinum chemotherapy and a network meta-analysis to add the pembrolizumab combination therapy. Both comparator arms were informed by the KEYNOTE-189 study.

a) Please confirm whether three treatment arms were compared in this manner.

Lilly can confirm that a propensity score matching analysis was used only for the comparison of the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial with the LIBRETTO-001 selpercatinib arm only.[20, 46] As outlined in response to Part a) of Question 21, this was due to the IPD being available for this arm of the KEYNOTE-189 arm only.

b) Please justify that two different methods were used to model the comparator arms.

As outlined in response to Part a) of Question B.9 above, only the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial had IPD available. As such, use of PSM to obtain relative treatment affects via an ITC could not be conducted on the pembrolizumab plus pemetrexed plus platinum chemotherapy arm of the KEYNOTE0189 trial. Therefore, the ITC of selpercatinib compared to pemetrexed plus platinum-based chemotherapy was used to connect selpercatinib to an NMA in order to obtain a relative treatment effect for selpercatinib compared to pembrolizumab combination therapy.

c) Please conduct a scenario analysis by modelling the pembrolizumab combination therapy by conducting a propensity score matching analysis (as with the pemetrexed + platinum chemotherapy arm).

As outlined in response to Part a) of this question above, it is not possible to conduct this scenario analysis, as there are no IPD for the pembrolizumab combination therapy arm available from the KEYNOTE-189 trial.[46] [20]

B10. In the company's base case, no treatment waning was assumed, i.e. a lifelong selpercatinib treatment effect was assumed.

a) Please justify the assumption of no treatment waning, i.e., that there is a lifetime selpercatinib treatment effect.

Lilly maintain that the exclusion of a treatment waning effect in the economic model is a suitable approach owing to the following reasons:

- **The LIBRETTO-001 trial does not provide evidence of relative treatment effect waning for selpercatinib.** The LIBRETTO-001 trial is a single arm study, and thus does not provide direct, head-to-head data on the relative efficacy of selpercatinib versus an active comparator.[25] As such, there is no clinical evidence to support that the treatment effect of selpercatinib relative to active comparators would be expected to wane over time. For this reason, the explicit application of a treatment waning effect for selpercatinib is not appropriate, and its implementation would rely on assumptions that could not be based on robust clinical data.

- **Different assumptions on the long-term treatment effect of selpercatinib would be implicitly captured in the selected survival curves.** As detailed in the response to Section B.4e) above, selection of the survival distribution utilised in the base case analysis was informed by landmark estimates provided by expert oncologists practicing in the NHS and survival estimates of ALK-positive patients treated with targeted therapies. One of the

clinical experts consulted advised that survival estimates for selpercatinib in *RET* fusion-positive patients could be deemed comparable to those of ALK-positive patients treated with targeted therapies.[9] Given that the long-term outcomes implemented within the model were confirmed by validated by UK clinicians as clinically plausible, Lilly consider that should any treatment effect waning be observed, it would be captured implicitly in the selected curves. As such, explicit application of treatment effect waning for selpercatinib is not appropriate.

- **Patients with *RET* fusion-positive advanced NSCLC have a poor prognosis.** There are limited published data on the survival of patients with advanced *RET* fusion-positive NSCLC, but real-world evidence from Mazieres et al. (2019) presented in Section B.1.2.1 of Company Submission indicates that median PFS for these patients ranged between 2.1–3.4 months, whilst median OS ranged between 10.0–21.3 months.[47] While selpercatinib is anticipated to improve patient outcomes, patients remain progression free for a relatively short period of time given the severity of the disease. Data more LIBRETTO-001 indicated patients treated with selpercatinib had a median PFS of 21.95 months at the latest data cut (OS data remained immature at the latest data cut).[6] As such, patients receiving selpercatinib are unlikely to experience treatment effect waning within their lifespan, and if they did, it would be highly unlikely to have a clinically meaningful impact due to the short time periods over which it could apply.

- **Selpercatinib is a continuous, treat to progression treatment.** Selpercatinib is administered until patients experience a progression event rather than for a prespecified period of time.[19] In addition, subsequent lines of therapy are included in the model. As such, patients are continuously receiving treatment throughout the model time horizon and thus the inclusion of treatment waning is not considered appropriate.

b) Please provide 1) hazard ratio plots for PFS and OS versus time for both comparisons as well as 2) hazard rate (smoothed) plots for PFS and OS over time for selpercatinib and both comparators, both with numbers of patients at risk over time to justify this assumption.

These plots are presented in response to Question B4 above. The propensity score matching Nelson-Aalen hazard rate plots for OS and PFS are presented in Figure 17 and Figure 18, respectively. The propensity score matching smoothed hazard rate plots for OS and PFs are presented in Figure 15 and Figure 16, respectively.

c) Please provide an updated economic model and scenario analyses exploring treatment waning at different time points.

As outlined in the response to question B.10 a) above, Lilly do not consider the explicit application of treatment waning in the economic model to be appropriate. As such, no updated economic analyses are presented.

B12. Section B.3.2.2 and B.3.2.3 of the company submission mention that cross-over between arms was allowed for the KEYNOTE-189 trial. However, it did not indicate that the analyses were adjusted for cross-over.

a) Please provide clinical effectiveness analyses of PFS and OS wherein treatment effectiveness is corrected for cross-over (consistent with the recommendations provided in NICE DSU TSD 16).

The OS data sourced from the KEYNOTE-189 trial to inform the pseudo-control arm were not adjusted for cross-over, as outlined in Gandhi et al (2018).[48] This paper states that the data for patients who crossed over from the placebo arm (pseudo-control arm) were not censored at the time of crossover for overall survival. In the placebo-combination group, 67 of 206 patients (32.5%) had crossed over during the trial to receive pembrolizumab monotherapy after disease progression. An additional 18 patients (8.7%) had received immunotherapy outside the trial, which resulted in an effective crossover rate of 41.3% in the intention-to-treat population.

Utilisation of the unadjusted Kaplan-Meier data for the placebo arm from KEYNOTE-189 is likely to increase OS for the pseudo-control arm used in the ITC and produce more conservative HRs versus selpercatinib. However, overall, it is likely that the impact of crossover is negligible on the results produced from the ITC. As discussed in the response to Question A22) above, in the base case analysis the PSM method was ultimately selected for the adjustment process in the ITC as the results were associated with the highest external validity. Patients in the SAS1 population of the LIBRETTO-001 trial were typically younger and healthier than the advanced NSCLC more generally. As a result, the mean age and number of non-smokers for the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial were anticipated to be artificially reduced in the adjustment process, thus resulting in increased mPFS and mOS for this population.

b) Please provide an updated economic model and scenario analyses wherein treatment effectiveness is corrected for cross-over.

Due to time constraints, Lilly were unable to provide the requested analysis adjusting the pemetrexed plus platinum-based chemotherapy arm for crossover. However, as outlined in Part a) above, it is not anticipated that adjusting for crossover would have a major impact on the results of the ITC. Further to this, the results of the base case analysis using the unadjusted PSM approach produced externally valid and clinically plausibly OS results for the pemetrexed plus platinum-based chemotherapy arm.

Adverse events

B13. Priority question: As discussed in clarification question B2 above, comparators that were described as relevant in the NICE scope have not been included in the economic model (i.e., pembrolizumab monotherapy,

atezolizumab, atezolizumab plus bevacizumab, carboplatin and paclitaxel and chemotherapy).

a) Please update company submission Table 49 and include the incidence of grade 3-4 adverse events (AEs) for all relevant comparators included in the NICE scope.

As discussed in response to Question B2 above, pembrolizumab monotherapy, atezolizumab, atezolizumab plus bevacizumab, carboplatin and paclitaxel and chemotherapy are not considered to be relevant comparators to selpercatinib for this appraisal. Therefore, an updated table of adverse event incidence including for these comparators has not been provided.

b) Please update company submission Tables 51 and 64 and include the AE disutilities and costs for all relevant comparators included in the NICE scope.

As stated in response to Part a) of this question, these comparators are not deemed relevant to this appraisal and therefore an update to Table 51 and Table 64 has not been provided.

c) Please provide an updated economic model and scenario analyses including the above-mentioned AEs for all relevant comparators in the NICE scope.

As stated in response to Part a) of this question, these comparators are not deemed relevant to this appraisal and therefore these updated economic analyses have not been provided.

B14. Priority question: As per company submission, Table 51 and 64 show the AE disutilities and costs applied in the cost-effectiveness model, including AEs (i.e., ECG QT prolonged, Thrombocytopenia, Hepatitis Lab abnormalities, sepsis, acute kidney injury, urinary tract infection, decreased platelet count, decreased neutrophil count, severe skin reaction, and proteinuria) that were assumed to have a zero disutility and/or cost. In addition, some of the assumed AE durations were not sufficiently justified (e.g., a 15 days duration for hypertension).

a) Please justify the zero disutility and/or cost assumption for the AEs mentioned above. In addition, justify assumed durations for those AEs for which no clear source was reported. Please provide supporting evidence showing that these assumptions are consistent with relevant external data and/or expert opinion. In case of expert opinion, please provide a full description of the methods and results of the expert consultation conducted:

Lilly acknowledges that the application of zero disutility or costs associated with these adverse events represents a potentially arbitrary assumption within the model. However, this approach is line with those applied in prior technology appraisals in NSCLC and therefore, in the absence of external data to inform these inputs, was utilised for consistency.[1, 32-34] Without sufficient data, it was necessary to apply these assumptions for the purposes of the cost effectiveness analysis. It should be noted that only Grade 3–4 adverse events with **at least 2%** difference in frequency between interventions in the source trials were included. Therefore, only the AEs listed in Table 24 below were included in the cost effectiveness analysis.

Table 24: Incidence, duration, disutility and costs of Grade 3–4 adverse events for selpercatinib and relevant comparators included in the model

Adverse Event	Selpercatinib (N = [redacted])	Pembrolizumab + pemetrexed + platinum chemotherapy (N = 405)	Pemetrexed + platinum chemotherapy (N = 202)	Duration	Disutility	Cost (£)
Diarrhoea	[redacted]	5.19%	2.97%	5.530	−0.0468	4443.85
Hypertension	[redacted]	0.49%	0.00%	15.000	0.085	967.40
ECG QT prolonged	[redacted]	0.00%	0.00%	0.000	0	902.89
Fatigue	[redacted]	5.68%	2.48%	23.780	−0.07350	2886.14
Asthenia	[redacted]	6.17%	3.47%	23.780	−0.07350	2886.14
Vomiting	[redacted]	3.70%	2.97%	15.000	−0.085	4443.85
Alanine aminotransferase increased	[redacted]	0.00%	0.99%	14.660	−0.0509	4231.62
Aspartate aminotransferase increased	[redacted]	0.00%	0.00%	14.660	−0.0509	4231.62
Hyponatraemia	[redacted]	0.25%	0.99%	15.000	−0.085	0.00
Lymphopenia	[redacted]	0.00%	0.00%	15.000	−0.05	4517.24
Pneumonia	[redacted]	5.68%	8.42%	15.000	−0.008	2465.50
Thrombocytopenia	[redacted]	7.90%	6.93%	0.000	0	3100.40
Neutropenia	[redacted]	15.80%	11.88%	15.000	−0.090000	3181.31
Anaemia	[redacted]	16.30%	15.35%	23.780	−0.07346	1363.57
Febrile neutropenia	[redacted]	5.68%	1.98%	15.000	−0.090000	5848.60
Pneumonitis	[redacted]	2.96%	1.98%	15.000	−0.085	3997.83
Nausea	[redacted]	3.46%	3.47%	15.000	−0.085	4443.85
Source	LIBRETTO-001[20]	KEYNOTE-189[39]	KEYNOTE-189[39]	-	-	-

b) If deemed appropriate, please provide an updated economic model and scenario analyses exploring different disutilities, duration, and costs for the abovementioned AEs for all comparators relevant to the NICE scope.

As outlined in response to Part a) above, Lilly considers the base case approach to modelling adverse events to be appropriate. Further to this, the results of the deterministic sensitivity analyses presented in Section B.3.10.2 of the Company Submission showed that the uncertainty around the assumptions relating to the duration of AEs, exclusion of costs and exclusion of disutilities had minimal impact to the cost effectiveness results. The results of this analysis versus pemetrexed plus platinum-based chemotherapy are presented in Table 25. The absolute change in the ICER for the cost per event for adverse events (selpercatinib) was less than £3,000 per QALY gained. As a result, an updated economic mode containing scenario analyses exploring different disultitlies, duration and costs for the abovementioned AEs has not been provided.

Table 25: Scenario analysis results for costs and disutilities associated with adverse events

	ICER (£/QALY gained)		Cost-effectiveness quadrant[a]		Absolute change in ICER (£)
	Lower bound	Upper bound	Lower bound	Upper bound	
Adverse Event Costs - Cost per Event - Selpercatinib	37,427	34,461	Q1	Q1	2,966
Adverse Event Costs - Cost per Event - Progressed disease	35,190	36,576	Q1	Q1	1,386
Adverse Event Costs - Cost per Event - Progression-free	35,339	36,427	Q1	Q1	1,088

[a] *The quadrant where the ICER falls: Q1 = quadrant 1; Q2 = quadrant 2 (intervention dominated); Q3 = quadrant 3 (less expensive and less effective); Q4 = quadrant 4 (intervention dominates) **Abbreviations:** AE: adverse event; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year.

B15. The incidence of grade 3-4 AEs for selpercatinib and relevant comparators included in the model were reported in company submission Table 49. According to the footnote, the model also includes AEs from other trials which are currently not presented in the table. Please provide an updated Table 49 also including AEs from other trials that were incorporated in the economic model.

Lilly thank the ERG for highlighting this and can confirm that this is an error in the footnotes of Table 49 of the submission; the model does not include any AEs related to non-relevant comparators or any AE data from alternative trials. The updated table, with corrected footnotes has been provided below (Table 26).

Table 26. Incidence of Grade 3–4 adverse events for selpercatinib and relevant comparators included in the model

Adverse Event	Selpercatinib (N = 69)	Pembrolizumab + pemetrexed + platinum chemotherapy (N = 405)	Pemetrexed + platinum chemotherapy (N = 202)
Diarrhoea	[redacted]	5.19%	2.97%
Hypertension	[redacted]	0.49%	0.00%
ECG QT prolonged	[redacted]	0.00%	0.00%
Abdominal pain	[redacted]	0.00%	0.00%
Haemorrhage	[redacted]	0.00%	0.00%
Fatigue	[redacted]	5.68%	2.48%
Decreased appetite	[redacted]	1.48%	0.50%
Rash	[redacted]	0.00%	0.00%
Asthenia	[redacted]	6.17%	3.47%
Vomiting	[redacted]	3.70%	2.97%
Dyspnoea	[redacted]	3.70%	5.45%
Alanine aminotransferase increased	[redacted]	0.00%	0.99%
Aspartate aminotransferase increased	[redacted]	0.00%	0.00%
Hyponatraemia	[redacted]	0.25%	0.99%
Lymphopenia	[redacted]	0.00%	0.00%
Pneumonia	[redacted]	5.68%	8.42%
Dehydration	[redacted]	1.23%	0.99%
Thrombocytopenia	[redacted]	7.90%	6.93%
Neutropenia	[redacted]	15.80%	11.88%
Anaemia	[redacted]	16.30%	15.35%
Pleural effusion	[redacted]	1.48%	1.98%
Febrile neutropenia	[redacted]	5.68%	1.98%
Pyrexia	[redacted]	0.00%	0.00%
Pneumonitis	[redacted]	2.96%	1.98%
Nausea	[redacted]	3.46%	3.47%
Hepatitis Lab abnormalities	[redacted]	1.48%	0.00%
Hypothyroidism	[redacted]	0.00%	0.00%
Hyperthyroidism	[redacted]	0.00%	0.00%
Cellulitis	[redacted]	0.00%	0.00%
Sepsis[a]	[redacted]	0.00%	0.00%
Acute kidney injury[a]	[redacted]	0.00%	0.00%
Chronic obstructive pulmonary disease	[redacted]	0.99%	1.49%
Colitis	[redacted]	0.00%	0.00%

Adverse Event	Selpercatinib (N = 69)	Pembrolizumab + pemetrexed + platinum chemotherapy (N = 405)	Pemetrexed + platinum chemotherapy (N = 202)
Urinary tract infection	[redacted]	0.00%	0.00%
Peripheral neuropathy	[redacted]	0.00%	0.00%
Decreased platelet count	[redacted]	0.25%	0.00%
Decreased neutrophil count	[redacted]	0.00%	0.00%
Severe skin reaction	[redacted]	0.00%	0.00%
Proteinuria	[redacted]	0.00%	0.00%
Source	LIBRETTO-001	KEYNOTE-189[a]	KEYNOTE-189[a]

Abbreviations: AE: adverse event; ECG: electrocardiogram; NMA: network meta-analysis; NSCLC: non–small cell lung cancer; *RET*: Rearranged during transfection.
Sources: Eli Lilly and Company Ltd. Data on file. LIBRETTO-001 Clinical Study Report 2021 (15th June 2021 cut-off).[25] KEYNOTE-021.[49, 50] KEYNOTE-189.[51]

Quality of life

B16. Priority question. The company mapped EORTC QLQ-C30 data to EQ-5D data to inform health state utility values, because EQ-5D data were not collected in the LIBRETTO-001 trial. Four different mapping techniques were explored, resulting in different utility values for PF and PD (company submission, Table 50). The company stated that the mapping algorithm outlined by Young et al. (2015) produced the most plausible and lowest utility estimates, and were therefore conservatively chosen for the base case.

a) Please elaborate on thew conceptual overlap between EORTC QLQ-C30 and EQ-5D instruments.

The QLQ-C30 contains 30 questions covering the most common cancer symptoms, such as pain, fatigue, nausea, and vomiting, and various aspects of function including physical, role, social, emotional, and cognitive functioning. The QLQ-C30 is summarised using 14 scales, each representing a particular symptom or aspect of function, plus one global quality of life scale (based on two global questions).[52] Rowen *et al.* (2011) further derived a health state classification system based on QLQ-C30 with eight dimensions (physical functioning, role functioning, pain, emotional functioning, social functioning, fatigue and sleep disturbance, nausea, constipation and diarrhoea).[53] As such, the QLQ-C30 covers the five dimensions of the EQ-5D (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[54]

b) Please provide statistics regarding the correlation between the elements of the EORTC QLQ-C30 and EQ-5D instruments.

There are several published mapping functions for the EORTC QLQ-C30. Among them, McKenzie and van der Pol used ordinary least squares to predict EQ-5D-3L values.[55] Khan and Morris explored a number of alternative models for predicting EQ-5D in patients with lung cancer.[56]

For the submitted economic analysis, the work by Young et al. was used to map QLQ-C30 to EQ-5D. They report that assessment of the correlations between the EQ-5D and the QLQ-C30 scale scores indicated that the highest correlations are between physical functioning, role functioning, fatigue, and pain (r = 0.701, r = 0.688, r = −0.625, and r = −0.735, respectively).[54]

c) Please justify, considering the responses to the preceding subquestions, that it is appropriate to map the EQ-5D utilities from EORTC QLQ-C30 data.

Lilly note that as stated in Section 7.6 of the updated NICE manual, mapping is the next preferred alternative when EQ-5D data are not available.[57] As such, the mapping of the available QLQ-C30 data to EQ-5D utilities is in line with NICE preferences. Furthermore, a range of existing mapping algorithms were explored, since QLQ-C30 is one of the most commonly used scales in cancer studies and is frequently used for mapping into EQ-5D.

d) Please consider the ISPOR Good Practices for mapping studies (Wailoo et al. 2017 https://doi.org/10.1016/j.jval.2016.11.006) and provide detailed responses to all aspects/considerations mentioned in Tables 1, 2 and 3 of this paper.

With respect to Table 1 the of ISPOR Good Practices for mapping studies paper, Young et al. provide extensive justification on the pre-modelling consideration by describing the scales, data sets, purpose of the mapping work and patient characteristics in each set. They follow modelling and data analysis recommendations as laid out in Table 2 of the ISPOR guidelines by providing the rationale for selecting eight modelling approaches in their analysis. Furthermore, in Tables 2 and 3 of the paper, Young et al. comprehensively report the results and comparisons between the eight models and compare with other published mapping studies, in alignment with Table 3 of the ISPOR guidelines. As such, Lilly consider that the Young et al. paper to adhere to the ISPOR good practice guidelines laid out in Wailoo et al.

e) If deemed necessary, please provide an updated economic model and scenario analyses, incorporating an updated mapping function considering the ISPOR Good Practices for mapping studies.

For the reasons outlined above, an updated economic model and scenario analyses have not been provided.

B17. Priority question: In the company base case, health state utility values were informed by mapping EORTC QLQ-C30 data from the LIBRETTO-001 trial to EQ-5D data (PF=0.801, PD=0.749). Utility values sources from TA654 were explored in a scenario analysis (PF=0.794, PD=0.678). As per company

submission table 52 and 53, a small difference can be observed between the utility values of the PF and PD state.

a) The progressed disease decrement seems marginal in both the base case (0.052 decrement) and scenario analysis (0.071 decrement). Please provide justification for the small impact of disease progression in the utility values.

On average, patients in the SAS1 population of LIBRETTO-001 were younger than patients with NSCLC more broadly. One study collecting data from the Southend Lung Cancer Registry in the UK found that the median patient age at diagnosis of lung cancer was 71 years, and in Scotland, 89% of cases of lung cancer occur in patients over the age of 60 years.[28, 58] Furthermore, whilst there is a lack of data for the UK general population, in Scotland it has been found that roughly 90% of patients with lung cancer are also smokers or ex-smokers.[28] In contrast, the median age of patients in LIBRETTO-001 was 63 years, and the majority were non-smokers. This difference between the *RET*-fusion positive population and the broader NSCLC population is supported by clinical expert opinion received as part of the NICE appraisal of selpercatinib as a second-line therapy for patients with *RET*-fusion positive advanced NSCLC (TA760), where clinicians confirmed that these patients tend to be younger and have never smoked.[1]

As such, it is expected that these patients were generally better able to tolerate disease progression, and the subsequent therapies associated with it, and thus experience a relatively small utility decrement upon progression; the clinical experts consulted in TA760 concluded that patients with *RET*-fusion positive advanced NSCLC generally having higher utility values than people with other forms of lung cancer was feasible.[1]

b) Please elaborate on how the utility values from TA654 compare to those currently used in the economic model.

Regarding the progression-free HSUVs, the mapped values used in the economic model provide good comparability to those used in TA654 with an increment of only 0.007. However, Lilly acknowledge that there is large difference in the progressed disease HSUVs, with the mapped values from LIBRETTO-001 being higher than those from TA654. A possible reason for this is due to the limited number of post-progression observations – there were only [redacted] observations. However, a scenario analysis was presented in Section B.3.10.3 of the Company Submission in which HSUVs from TA654, which were accepted in the appraisal for pralsetinib, were implemented to explore this uncertainty.[59] The results of this scenario showed it had a limited impact to the base case results.

c) Please provide an updated model and scenario analyses exploring utility values from other relevant TAs (apart from TA654), such as TA306, TA428, TA476, TA484, TA520, TA557, TA584, TA621, and TA760, and elaborate on how these utility values compare to those currently used in the economic model.

Lilly acknowledge that utility values used in other previous NICE technology appraisals could be relevant for this appraisal. Scenario analyses are provided below where utility values sourced

from relevant Technology Appraisals, summarised in Table 27. These relate to targeted treatments at the same line of therapy as selpercatinib is intended to be used in the indication under consideration for this appraisal. As noted in response to Part a) of Question B17) above, patients with *RET*-fusion positive advanced NSCLC have unique characteristics compared to patients with NSCLC without a recognised genetic marker ,who would normally receive immunotherapy.

As stated in the Company Submission, utility values are applied to the progression-free and progressed health states to estimate HRQoL. As most responses to treatment with selpercatinib reported in the LIBRETTO-001 trial were partial responses, it was deemed unlikely that there would be an important improvement in HRQoL for responders as compared with non-responders. Therefore, no adjustment to the progression-free utility weight was made to reflect response in the base case.

In addition, in the base case analysis, HSUVs did not differ between treatment arms due to the lack of a control arm and lack of HRQoL data collected from LIBRETTO-001. As a suitable proxy for the scenario analysis, HSUVs were assumed to align with those accepted for TA654 for osimertinib in untreated EGFR mutation-positive NSCLC, which elicited HSUVs directly from clinical trial data.[32] The values accepted by the Committee were considered a suitable proxy for selpercatinib, being another targeted treatment in non-squamous NSCLC is a patient population similar to RET-fusion positive NSCLC.

The updated scenario analyses exploring utility values for other TAs are provided below in Table 28.

Table 27. Alternative HSUVs that could be suitable proxies for treatment-naïve *RET*-fusion positive patients

Scenario	HSUVs	Source	Justification	**Explored** in Scenario Analysis
1	PF: 0.794 PD:0.678	TA653 – Osimertinib	Data elicited directly from trials for patients for EGFR mutations on targeted treatment with osimertinib. PD values elicited from AURA2 for a ≥second line population which matches the impact of subsequent treatments on utility	Yes – Company preferred alternative HSUVs
2	PF: 0.784 PD: 0.517	TA310 – Afatinib PF: LUX-Lung 3 PD: Chouaid et al. 2013	PF values elicited directly from trial data for a targeted treatment in ALK, which could be considered another suitable proxy for selpercatinib. PD values based on a survey which included European patients which generated specific values for patients with progressed disease on second line treatment	Yes

3	PF: 0.814 PD non-CNS: 0.725	TA536 – Alectinib PF and PD: ALEX	ALK treatment considered a suitable proxy for selpercatinib. Direct elicitation of EQ-5D data from the pivotal trial – similar to Company base case HSUVs	Yes
4	PF: NR PD: 0.678	TA595 – Dacomitinib PF: EQ5D from ARCHER 1050 PD: TA563	Committee preferred HSUVs from TA563 for PD.	No
5	PF: 0.661 PD: 0.473	TA258 – Erlotinib Nafees et al. (2008)	Utilities in the model were based on values from the study of Nafees et al. (2008). These utility values were estimated using the standard gamble approach with 105 members of the UK general public who were asked to value health-state descriptions of patients receiving second-line chemotherapy for NSCLC. It should be noted that these values are based on an older study. Patients now have considerably more options at second line therefore the lower PD values may not be appropriate for this appraisal.	No - PD HSUV considered implausibly low for this patient population.
6	PF: 0.661 PD: 0.473	TA192 – Gefitinib	The EQ-5D was not used to measure HRQoL in pivotal trial (IPASS), the Company therefore undertook a review of the literature to identify relevant HRQoL data for use in the economic evaluation. The Company concluded that there was an absence of relevant utility estimates and adopted utility estimates from a single UK study by Nafees et al. (2008). It should be noted that these values are based on an older study. Patients now have considerably more options at second line therefore the lower PD values	No - PD HSUV considered implausibly low for this patient population.

			may not be appropriate for this appraisal.	
7	PF: 0.793 PD: 0.624	TA670 – Brigatinib	Derived from the EORTC QLQ C30 completed by patients enrolled in the ALTA-1L clinical trial using the mapping algorithm by Longworth et al. (2014)	Yes
8	PF: 0.81 PD: 0.68	TA500 – Ceritinib	PD HSUV is an average of PF and PD value calculated from (Chouaid et al. 2013). This accounted the patients either continuing treatment or switching treatment upon progression.	Yes
9	PF: 0.810 PD: 0.641	TA406 – Crizotinib	PF calculated from EQ5D collected from PROFILE-14 trial. PD from (Chouaid et al. 2013)	Yes
10	PF: 0.73 (ERG scenario 0.82) PD: 0.66	TA643 – Entrectinib	Similar trial design to LIBRETTO-001. PF estimated from utility data collected in the STARTRK-2 trial using the EuroQoL 5-dimension questionnaire with 3 scoring levels (EQ-5D-3L). Insufficient data from trial (STARTRK-2) to estimate PD therefor Company used HSUVs from TA529, which were sourced from the PROFILE 1007 trial with a population of ALK+ NSCLC patients whose disease had progressed after first-line treatment	No - PF HSUVs lower than accepted in TA760 (Selpercaintib for pre-treated RET-fusion positive NSCLC)
11	PF:0.719 PD:0.638	TA789 – Tepotinib	EQ-5D values were derived from a relevant METex14 patient population from the VISION trial where the 5L version was collected	No - PF HSUVs lower than accepted in TA760 (Selpercatinib for pre-treated RET-fusion positive NSCLC)

Abbreviations: ALK: Anaplastic lymphoma kinase; HSUVs: health state utility values; PD: progressed disease; PF: progression-free; NR: Not Reported; NSCLC: non-small cell lung cancer; SE: standard error; TA: technology assessment; EGFR: ERG: evidence review group.

Table 28. Scenario analysis results– alternative utility values from previous NICE Technology Appraisals in NSCLC

Scenario		Selpercatinib vs pembrolizumab + pemetrexed + platinum chemotherapy			Selpercatinib vs pemetrexed + platinum chemotherapy		
		Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	***5,264***	[redacted]	[redacted]	***35,883***
1	TA310 Afatinib HSUVs	[redacted]	[redacted]	6,253	[redacted]	[redacted]	41,985
2	TA536 Alectinib HSUVs	[redacted]	[redacted]	5,299	[redacted]	[redacted]	36,046
3	TA670 Brigatinib HSUVs	[redacted]	[redacted]	5,750	[redacted]	[redacted]	38,897
4	TA500 Ceritinib HSUVs	[redacted]	[redacted]	5,471	[redacted]	[redacted]	37,116
5	TA406 Crizotinib HSUVs	[redacted]	[redacted]	5,619	[redacted]	[redacted]	38,019

Abbreviations: HCRU: healthcare resource use; ICER: incremental cost-effectiveness ratio; Incr: incremental; N/A: not applicable; OS: overall survival; PFS: progression-free survival; TTD: time-to-treatment discontinuation.

B18. Priority question: The modelled utility for the pre-progression health state was 0.801 in the company base case, which is only slightly under the UK general population norm for this age group (0.819 for 55-64 years, Szende et al. 2014). Please elaborate on how the estimated health state utilities values (reported in company submission Table 52 and 53 and based on the responses provided above) compare with UK general population utilities (matched for age and gender) and elaborate on the implications for the results. Please provide an updated economic model and scenario analyses capping the PF utility value based on these UK general population utility values.

Lilly acknowledge that the utility values utilised in the base case analysis for the pre-progression health state were close to the general population norm for this age group. However, as outlined in response to Part a) of Question B17 above, *RET*-fusion positive patients are generally younger and healthier (non-smoking) than the broader UK NSCLC population, and this is observed in patients included in the SAS1 population of the LIBRETTO-001 trial. Therefore, it is expected that the utility values of patients in the SAS1 population would be closer to the general population utility than patients with other forms of lung cancer would experience.

The view that *RET*-fusion positive patients typically have higher utility values than patients with other forms of lung cancer was supported by feedback received from clinical experts consulted during TA760.[1] The progressed health state utilised in the base case analysis was not

considerably lower than the PF health state given the expectation that *RET*-fusion positive patients would generally be better able to tolerate disease progression, and the subsequent therapies associated with it. The use of higher utility values compared to the NSCLC population for PD for *RET*-fusion positive patients was accepted by the Committee in TA760.[1]

Furthermore, as outlined in Section B.3.3.5 of the Company Submission, in order to assess uncertainty surrounding the utility values used in the economic model, a scenario analysis was explored in which utility values were derived directly from data elicited from trials in patients on other targeted NSCLC treatments. As expected, the utility values used for the PF and PD disease in this scenario were lower than those utilised in the base case analysis as they were not obtained from *RET*-fusion positive patients.

While Lilly acknowledges the propensity of the base case mapped PF HSUVs to the general population average, due to time constraints the scenario requested by the EAG could not be implemented in the economic model.

However, it is anticipated that the impact of the requested scenario analysis to the base case results would be minimal. [redacted]% of progression-free LYs (discounted) are gained (versus pembrolizumab combination therapy) in first three years. The simulation starts with mean age of 61.5, meaning that after three years, the patients are 64.5 years old, on average. Furthermore, by the age of 74 years, only [redacted]% are progression free (calculated using the Company base case distribution of Gompertz). If the weighted mean of the UK population norms for age groups 55–64 years (56%) and 65–74 years (44%) are calculated, the result is 0.804, which is still higher than the value of 0.801 used in the model. Using the same proportions, the capping (to 0.785) after three years would result in an average utility of 0.794 (versus 0.801). This is the same PF HSUV explored in the originally submitted scenario analysis (Company Submission, Section B.3.10.3) in which the HSUVs from TA654 are applied. As such, the scenario analysis presented in the Company Submission is sufficient to explore the uncertainty around the Company base case mapped HSUVs.

B19. As per company submission, EORTC QLQ-C30 questionnaires were completed on different timepoints by patients in the LIBRETTO-001 study. To assess the potential impact of missing values, please provide a table including the number of patients that were expected to complete the questionnaires per timepoint, the number of patients that actually completed it per timepoint, and the absolute and relative number of missing data per timepoint.

Of the [redacted] patients in the SAS1 cohort of LIBRETTO-001, [redacted] ([redacted]) completed the baseline assessment. Per protocol, only these patients were eligible for the EORTC QLQ-C30 analysis. Compliance of these patients over time is summarised in Table 29 below.

Table 29. Return rates for EORTC-QLQ-C30

Endpoint	Return rates for pre-planned evaluations (%)
Baseline	[redacted]
Cycle 3, Day 1	[redacted]
Cycle 5, Day 1	[redacted]

Cycle 7, Day 1	[redacted]
Cycle 9, Day 1	[redacted]
Cycle 11, Day 1	[redacted]
Cycle 13, Day 1	[redacted]
Cycle 16, Day 1	[redacted]
Cycle 19, Day 1	[redacted]
Cycle 22, Day 1	[redacted]
Cycle 25, Day 1	[redacted]
Cycle 28, Day 1	[redacted]
Cycle 31, Day 1	[redacted]
Cycle 34, Day 1	[redacted]
Cycle 37, Day 1	[redacted]
End of Treatment	[redacted]

Footnotes: Return rate is defined as percent of patients who have returned the questionnaire out of all patients with the visit at the specified cycle.
Abbreviations: EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Core Quality of Life Questionnaire C30.

Costs and resource use

B20. Priority question: In company submission Table 54, which summarises drug acquisition costs for selpercatinib and relevant comparators, there seems to be a discrepancy in the reporting of carboplatin costs (i.e., different costs per pack are reported for the same strength/unit and pack size). Please justify this potential discrepancy, and if needed, please correct the economic model accordingly.

Lilly thank the EAG for highlighting this and can confirm that this is an error in Table 54 of the submission. The updated table, with the updated values underlined, has been provided below (Table 30).

Table 30: Drug acquisition costs for selpercatinib and relevant comparators (pembrolizumab + pemetrexed + platinum chemotherapy and pemetrexed + platinum chemotherapy) (corrected Table 54 from the Company Submission)

Treatment	Form	Strength/unit	Pack size	Cost per pack (£)	Source
Selpercatinib					
Selpercatinib	Capsules	80 mg	60	[redacted]	Eli Lilly and Company. Data on file. Including PAS discount.
Selpercatinib	Capsules	40 mg	60	[redacted]	Eli Lilly and Company. Data on file. Including PAS discount.
Pembrolizumab + pemetrexed + carboplatin					

Pembrolizumab	Vial	100 mg	4 ml	2,630.00	BNF (2022)
Pemetrexed	Powder	100 mg	1	128.00	BNF (2022)
Carboplatin	Vial	150 mg	15 ml	6.08	eMIT (2021)
Pemetrexed + platinum chemotherapy					
Pemetrexed	Powder	100 mg	1 ml	128.00	BNF (2022)
Carboplatin	Vial	150 mg	15 ml	6.08	eMIT (2021)

Abbreviations: BNF: British National Formulary; eMIT: Electronic market information tool; PAS: Patient Access Scheme.
Source: BNF (2021);[60] eMIT (2021).[61]

B21. Priority question: After discontinuation of their initial treatment, patients in the economic model were assumed to receive a subsequent line of therapy. In the company's base case, the distribution of subsequent treatments was informed by subsequent treatment distributions in TA584, TA531 and TA484 (involving other targeted treatments in non-squamous NSCLC). In addition, a scenario analysis was explored using expert oncologist values to inform the proportions of subsequent treatments.

a) Please justify the differences in subsequent treatment distribution from TAs 584, 531, 484 and the values informed by the expert oncologist, and elaborate on the appropriateness of both sources (i.e., why was the subsequent treatment distribution based on other TAs deemed more appropriate than the values reported by the expert oncologist).

For consistency, the distribution of subsequent treatments in the base case analysis were aligned with the subsequent treatment distributions implemented and accepted in prior NICE technology appraisals in NSCLC (TA584, TA531, and TA484).[62-64] These appraisals were deemed appropriate given immunotherapy (pembrolizumab combination therapy) was a main comparator for this appraisal. As such, Lilly maintain that the distribution of subsequent treatments informing the submitted economic approach is appropriate.

However, Lilly acknowledge that the patient populations in these appraisals are not fully aligned with the population in this submission. For this reason, a scenario analysis provided as part of the Company Submission was conducted in which the proportions of subsequent treatments were informed by an expert oncologist considering adults with advanced *RET* fusion-positive NSCLC not previously treated with a RET inhibitor, specifically (see response to Part b) of this question, below).

b) Based on the expert oncologist, a substantial proportion of patients is expected to receive best supportive care as subsequent line of therapy. Please justify why best supportive care was not part of the base case subsequent treatment distribution.

As outlined in response to Part a) of this question, subsequent treatments for NSCLC following first-line therapy in the base case analysis were informed by prior NICE technology appraisals (TA584, TA531, and TA484).[62-64] While Lilly acknowledge that the exclusion of best supportive care (BSC) as a subsequent treatment option from the base case analysis is a potential limitation of the current model, a scenario analysis was conducted and presented in Section B.3.10 of the Company Submission in which subsequent treatment distributions were based on clinical expert opinion. In this scenario, best supportive care as well as docetaxel plus nivolumab nintedanib and pemetrexed plus platinum chemotherapy were included as subsequent treatment options. The results of this scenario analysis are presented in Section B.3.10.3 of the Company Submission. The inclusion of BSC and other additional treatments increased the ICER by around £3,500/QALY for pemetrexed plus platinum chemotherapy while it reduced the ICER by £100/QALY for pembrolizumab combination therapy, as compared with the base case approach.

c) Please elaborate on how the subsequent therapy distributions that were utilised in both the company base case analysis and the scenario analysis (summarised in Table 60 and Table 61), align/compare with the care pathway for RET fusion positive advanced NSCLC in NICE guideline 122.

Docetaxel and nintedanib, nivolumab, pembrolizumab, and atezolizumab are included in the care pathway for *RET* fusion-positive advanced NSCLC in NG122, but at positions in the pathway other than after treatment with selpercatinib.[30] Therefore, the exclusion of these therapies as subsequent therapies in the submitted approach is in alignment with NG122.

Pemetrexed plus platinum chemotherapy is not included as a subsequent treatment in NG122 but was included the submitted approach. This inclusion was based on feedback from the clinical validation with the expert oncologist, who noted that mono-immunotherapies are less effective for patients with *RET* fusion-positive NSCLC and thus that subsequent treatment with chemotherapy and pemetrexed is more appropriate for these patients.[11]

In the care pathway in NG122, selpercatinib is included as a subsequent treatment.[30] However, selpercatinib as a subsequent, second-line treatment is currently in the CDF. Therefore, in alignment with NICE guidance that drugs currently funded via managed access agreements such as the CDF are not relevant to include as comparators, selpercatinib was not considered as a subsequent treatment.[57]

Finally, best supportive care (BSC) was not included as a subsequent treatment in alignment with its exclusion from the care pathway in NG122.[30]

d) In the company's base case analysis, docetaxel and nintedanib, nivolumab, pembrolizumab, atezolizumab, and selpercatinib were not part of the modelled subsequent therapies, even though these are listed as second-line treatment options in the care pathway for RET fusion positive advanced NSCLC in NICE guideline 122. Please justify this potential mismatch between the modelled subsequent treatments and the care pathway for RET fusion positive advanced NSCLC in NICE guideline 122.

Docetaxel plus nintedanib, nivolumab monotherapy, pembrolizumab and atezolizumab are included as subsequent treatment options for *RET*-fusion positive patients in the NICE guideline 122, but they are not suggested as subsequent therapies following selpercatinib. Feedback received from UK expert oncologists who treat *RET*-fusion positive patients in clinical practice noted that immunotherapies alone are less effective in *RET* fusion positive patients and therefore their use in clinical practice is limited.[9] This feedback is consistent with real-world evidence findings by Offin et al. (2019) which concluded that *RET*-fusion positive tumours are less likely to be responsive to immunotherapies relative to other cancers.[10] In addition, the expert oncologists noted that it is not anticipated that any patients would receive docetaxel plus nintedanib or nivolumab monotherapy following treatment with selpercatinib (see Table 61 of the Document of the Company Submission). As such, Lilly maintain that these treatments are not relevant subsequent treatments for patients receiving selpercatinib.

Furthermore, Lilly wish to highlight that in acknowledgement of this point, the scenario analysis discussed in Part c) of this question above, which was presented in Section B.3.10.3 of the Company Submission, included docetaxel plus nintedanib, nivolumab monotherapy, pembrolizumab and atezolizumab as subsequent treatment options for patients not receiving selpercatinib first line. The results of this scenario altered the ICERs by less than £4,000/QALY, indicating this not to be a significant model driver.

Regarding selpercatinib, as outlined in the response to Part a) of this question above, selpercatinib as a second-line treatment is currently funded via the CDF. In alignment with NICE guidance that drugs currently funded via managed access agreements such as the CDF are not relevant to include as comparators, selpercatinib was not considered as a subsequent treatment in the Company submisison.[57]

e) In the company's scenario analysis, the subsequent therapies based on the expert oncologist values did not include docetaxel, docetaxel and nintedanib, and nivolumab as subsequent treatments for selpercatinib, even though these are listed as second-line treatment options in the care pathway for RET fusion positive advanced NSCLC in NICE CG122. Please justify these potential mismatches between the modelled subsequent treatments and the care pathway for RET fusion positive advanced NSCLC in NICE guideline 122.

The subsequent therapies included in the scenario analysis presented in the Company Submission were based on the opinion of the expert oncologists. This was informed by their direct experience of treating *RET* fusion-positive patients in UK clinical practice, but they were not specifically asked to provide reasoning as to why their clinical decisions may not align in full with the recommendations laid out in NICE guideline 122. However, the oncologists noted that immunotherapy alone following treatment with selpercatinib is not a particularly effective treatment option for *RET* fusion-positive patients and therefore its use is limited where possible. Furthermore, it was noted that nivolumab is rarely used as a subsequent treatment after selpercatinib for *RET* fusion-positive patients. Based on these comments, these subsequent therapies were not included in the Company's scenario analysis, in order to better reflect use in typical current UK clinical practice.

f) Please provide an updated economic model and scenario analysis including (appropriately distributed) subsequent treatments aligned with the NICE care pathway for non-squamous RET fusion-positive NSCLC patients.

As outlined above, Lilly maintain that the subsequent treatments included in the submitted economic analysis are appropriate, and have provided scenario analyses which support that this is not a key model driver. For this reason, an updated economic model and scenario analyses have not been provided.

B22. Resource use by the health state in the base case was informed by the previous technology appraisal TA654 for osimertinib in EGFR mutation-positive NSCLC as summarised in Table 62. While in a scenario analysis, it was provided by an expert as reported in Table 63. Please provide a justification of the slightly higher resource use in progression free states of the disease when compared to the progressed states as seen in both Table 62 and Table 63.

Clinical expert feedback received by Lilly supports the marginally higher resource use implemented in progression free states as compared with resource use in the progressed states: the clinician noted that the majority of medical imaging takes place pre-progression.[11] As such, it retains clinical plausibility that the imaging frequencies for patients with progressed disease would be lower than the frequency for pre-progression patients.

Results

B23. Priority question: Considering the company submission base case results.

a) Please provide a comparison of the observed OS as well as progression free survival (e.g. using restricted mean survival time; RMST) and the modelled undiscounted life years (LYs) as well as modelled undiscounted progression free LYs by completing the Table below using different periods/truncation points (with justification) to calculate the RMST. Please complete this Table once with pemetrexed + platinum chemotherapy as comparator and once with pembrolizumab + pemetrexed + platinum chemotherapy as comparator.

Please find the requested RMST analysis for selpercatinib and pemetrexed plus platinum-based chemotherapy in Table 31. There were no KM data available for the pembrolizumab combination therapy comparator in the economic model as HRs were applied for this comparison. Therefore, Lilly are unable to complete the RMST analysis for this comparator.

Table 31. Comparison of the observed OS and PFS, modelled undiscounted life years and modelled undiscounted progression free life years

	Observed	Modelled	
	Restricted mean survival time (RMST)	Estimated (lifetime time horizon)	Proportion beyond observed data[a]
OS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])			
Selpercatinib	[redacted]	[redacted]	[redacted]
Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	
OS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
Selpercatinib	[redacted]	[redacted]	[redacted]
Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])			
Selpercatinib	[redacted]	[redacted]	[redacted]
Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
Selpercatinib	[redacted]	[redacted]	[redacted]
Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

[a] Proportion beyond observed data is calculated as 100% - [Restricted mean survival time (RMST)/ Estimated (lifetime time horizon) *100] [b] For PFS restricted mean survival, the maximum observed time in Keynote189 control arm is 17.741, this is the time used for both Selpercatinib and Pemetrexed+Platinum in the calculation. The estimate is unreliable at the tail for the Pemetrexed+Platinum RMST.
Abbreviations: OS: overall survival; PFS: progression free survival; RMST: restricted mean survival time.

b) Please elaborate on the plausibility of the differences between observed and modelled outcomes (proportion accumulated beyond observed data) for:

i. selpercatinib

ii. pemetrexed + platinum chemotherapy

iii. pembrolizumab + pemetrexed + platinum chemotherapy

iv. the increment (selpercatinib versus pemetrexed + platinum chemotherapy)

v. platinum chemotherapy

Lilly would like to highlight that it is difficult to draw conclusions on the fit of the modelled versus observed data using the figures provided above and thus for Lilly to comment on the plausibility of the differences between the observed and modelled outcomes. The proportions beyond the observed data or the remaining life-years beyond the chosen truncation points provides information on the relative maturity of the data and on the reliance of decision-making on the extrapolated period. To assess fit of modelled versus observed data, assessment of statistical fit using AIC and BIC statistics is better suited. As stated throughout this response document, the survival data for PFS and OS are relatively immature for selpercatinib. In addition, it is expected that proportions of the life-years remaining and calculated by the extrapolated period from the economic model will be larger in comparison to the RMST calculated at the chosen truncation points, given that the shorter the truncation point, the larger the proportion will be. For this reason, Lilly held greater weight to the external validity of extrapolations to guide model choice in the Company base case (see response to Part i) of Question B4).

Therefore, Lilly caution against the use of this type of analysis to inform uncertainty in the extrapolations as it does not provide any information on the clinical plausibility of the long-term extrapolations.

c) Regarding the modelled estimated differences between the intervention and the comparator (in terms of PFS, LYs and quality-adjusted life years (QALYs)); please provide an explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence (NICE DSU TSD 19 recommendation 13).

Please refer to Table 73 in the Company submission where an assessment of external validity of the modelled outcomes compared to available external evidence is presented.

d) Please also complete the abovementioned questions for all other comparators mentioned in the scope.

There were no KM data available for the pembrolizumab combination therapy comparator in the economic model as HRs were applied for this comparison. Therefore, Lilly are unable to complete the RMST analysis for this comparator.

B24. The cost effectiveness analyses do not consider subgroups. Please justify why the subgroup(s) mentioned in company submission Table 1 is/are not considered in the cost effectiveness analyses.

Table 1 of the Company submission refers to the following three subgroups:

- Level of PD-L1 expression
- Tumour histology (squamous or non-squamous)
- Patients with Investigator assessed CNS metastases at baseline

Given that PD-L1 status was not collected in the pivotal LIBRETTO-001 trial, subgroup analyses of patients based on PD-L1 expression could not to be performed. Similarly, all treatment-naïve patients with advanced *RET*-fusion positive NSCLC enrolled in the LIBRETTO-001 trial had non-squamous histology, so subgroup analyses by tumour histology could not be performed. In addition, as selpercatinib is anticipated to be a treatment option for all *RET*-fusion positive advanced treatment-naïve NSCLC patients, regardless of their PD-L1 status or tumour histology, subgroup analyses by PD-L1 status or tumour histology are not relevant to the decision problem.

As described in response to Question A16 above, clinical subgroup analyses in patients with Investigator assessed brain metastases were carried out in the LIBRETTO-001 trial owing to the high prevalence of brain metastases in patients with *RET* rearrangements and the detrimental impact of brain metastases on survival.[17] However, a subgroup analysis in this patient population was not included in the economic model as differential efficacy of selpercatinib in this subgroup of patients compared with *RET*-fusion positive patients without brain metastases is not anticipated, and thus its inclusion was not appropriate. The exclusion of this subgroup from the economic model is in line with prior appraisals in NSCLC.[7, 34]

Validation and transparency

B25. Priority question: The company submission refers to expert opinion on multiple occasions to support and/or validate components of the health economic model.

a) Please provide supporting documents for the expert meetings and/or advisory board meetings, i.e., the minutes/input obtained from this meeting and how the expert opinion was gathered.

The meeting minutes from the clinical validation with the expert oncologists was cited as Reference 17 in the Company Submission and were included in the reference pack provided alongside the main submission. However, for ease of reference and transparency, these minutes have been incorporated into the reference pack submitted alongside these clarification question responses, as has the slide set used for the clinical validation meeting.[11]

b) Please clarify why the experts were considered to qualify as experts to address these questions.

Both clinicians consulted by Lilly are Consultant Medical Oncologists working in large hospitals in the UK and are lecturers at NHS Hospital Foundation Trusts. For further details, including the names and workplaces of the clinicians, please refer to Page 4 of the clinical validation meeting minutes.[9]

B26. Priority question: The results of the validity assessments are not described nor are detailed validation exercises (i.e., specific black-box tests) described.

a) Please provide a detailed description of the validity assessment performed as well as the results.

A technical validation of the cost-effectiveness model for selpercatinib in treatment-naïve patients with advanced *RET* fusion positive NSCLC was conducted. A model sanity checklist was followed which "stress-checked" the model by setting extreme scenarios to check that the model responded in the appropriate fashion. All changes to the model were made by a health economist and each change made after the performance of the stress test were quality controlled by a second health economist. The stress checklist used to validate the model and the results of the test are provided in Appendix E. The results indicated that the model behaved as expected and passed all of the stress tests implemented.

In addition, an in-depth cell by cell verification of the model to ensure that all formulae, inputs, linkages and macros were correctly implemented was performed. Overall, a minimal number of major errors were identified during the technical validation and these were subsequently updated in the cost-effectiveness model submitted to NICE.

b) Please complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.

The sanity checklist described in Part a) above was derived based on the TECH-VER checklist and thus provided the same verification of validity as the TECH-VER checklist. As such, a completed TECH-VER checklist has not been provided.

B27. In company submission Figures 32 and 33, the bars for both the lower and upper bound for some input parameters move in the same direction. Generally, it is expected that the lower bound of a parameter increases the ICER and the upper bound of a parameter decreases the ICER or vice versa. Please clarify these counterintuitive results.

The company thank the ERG for noting this and can confirm that this was an error. This error has been corrected in the model submitted alongside this document. The updated tornado diagrams containing the correct values are presented below (Figure **20** and Figure 21).

Figure 20. DSA tornado diagram for selpercatinib vs pembrolizumab combination therapy

Abbreviations: DSA: deterministic sensitivity analysis; ECG: electrocardiogram

Figure 21. DSA tornado diagram for selpercatinib vs pemetrexed plus platinum-based chemotherapy

Abbreviations: DSA: deterministic sensitivity analysis; ECG: electrocardiogram

B28. The probabilistic analyses require a relatively long run time (as also mentioned in company submission section B.3.10.3). Please clarify whether there are straightforward adjustments that the EAG can incorporate to speed up the probabilistic analyses.

Unfortunately, due to the application of a macro to generate cost effectiveness results on every iteration, there are no straightforward adjustments that were found to speed up the run time of the probabilistic analyses.

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Appendix A: Subsequent therapies of patients in the LIBRETTO-001 trial

Table 32. Summary of subsequent therapies of patients in the LIBRETTO-001 trial

Type of anti-cancer therapy	SAS1 patients ([redacted]), n (%)	SAS1 patients who received subsequent therapy ([redacted]), %
Chemotherapy	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
TS-1	[redacted]	[redacted]
Avastin	[redacted]	[redacted]
Carbo/pembrolizumab	[redacted]	[redacted]
Carbo/peme/bev	[redacted]	[redacted]
Carboplatin, pemetrexed, pembrolizumab	[redacted]	[redacted]
Carboplatin, pemetrexed, and pembrolizumab	[redacted]	[redacted]
Carboplatin/pemetrexed/pembrolizumab	[redacted]	[redacted]
Maintenance pemetrexed and pembrolizumab	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Pemetrexed (Alimta)	[redacted]	[redacted]
Pemetrexed/pembrolizumab	[redacted]	[redacted]
Targeted therapies	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]
BLU-667	[redacted]	[redacted]
ADC68, PDNA, tremelimumab and PF-06801591	[redacted]	[redacted]
Cabozantanib	[redacted]	[redacted]
Pembrolizumab (keytruda)	[redacted]	[redacted]
Radiation to the right lung 5000CGY ended on 01/15/2020	[redacted]	[redacted]
Other	[redacted]	[redacted]
Avastin	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]

Abbreviations: SAS1: supplementary analysis set 1.

Appendix B: Programming language utilised for the adjustment techniques to generate the pseudo-control arm

Figure 22: Programming language utilised for PSM

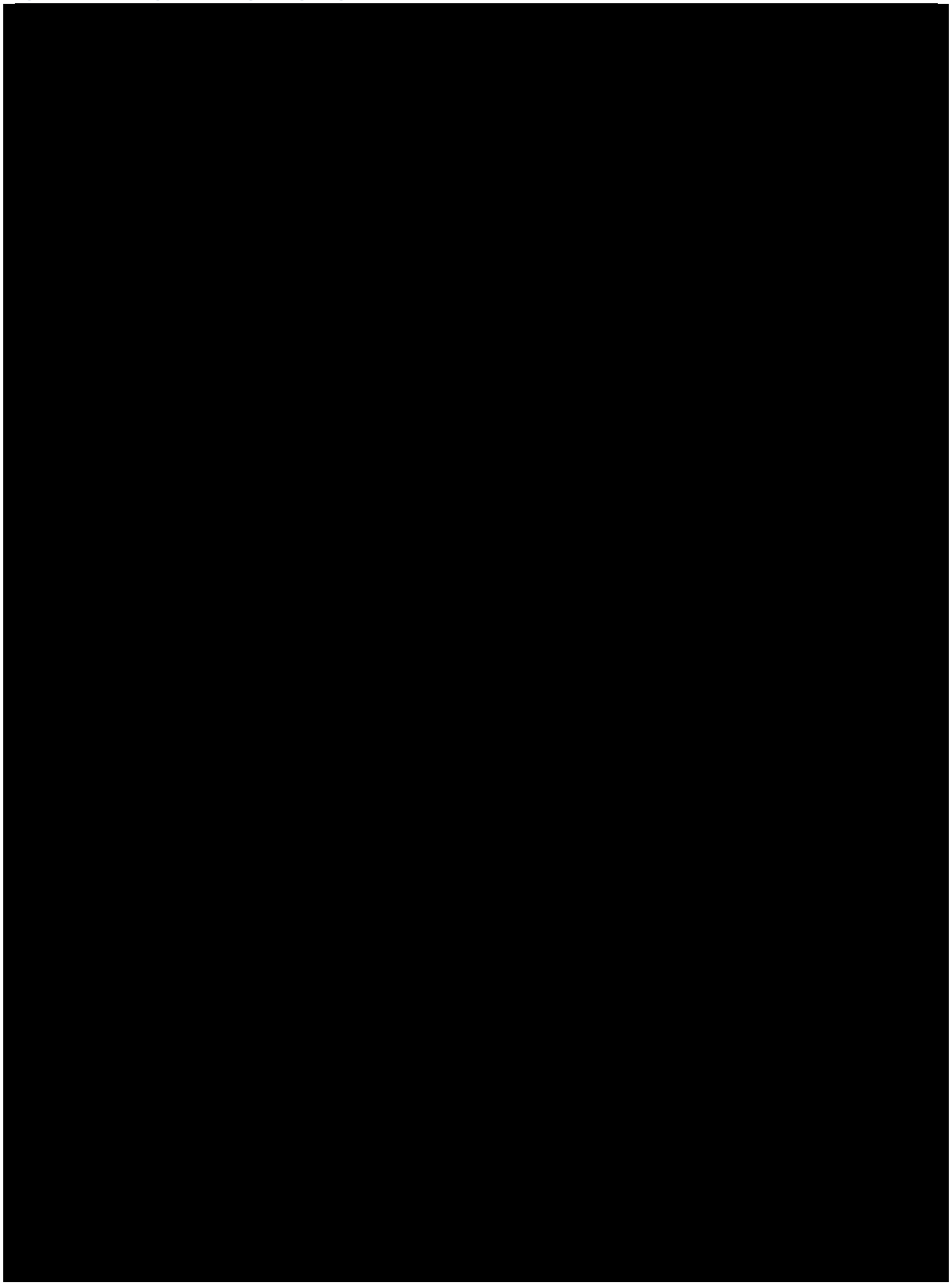


Figure 23: Programming language utilised for genetic matching

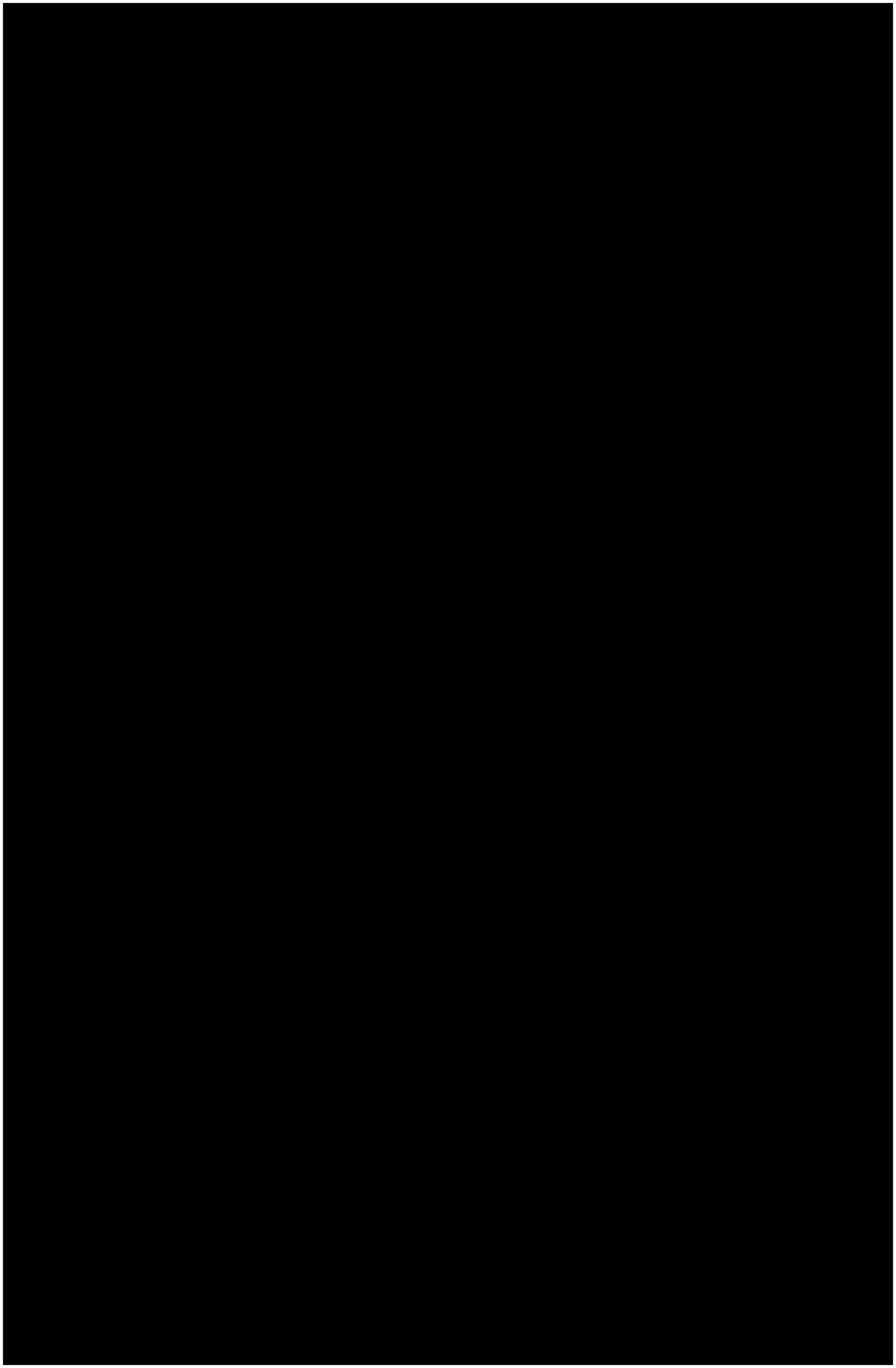


Figure 24: Programming language utilised for PSW using a generalised boosted model

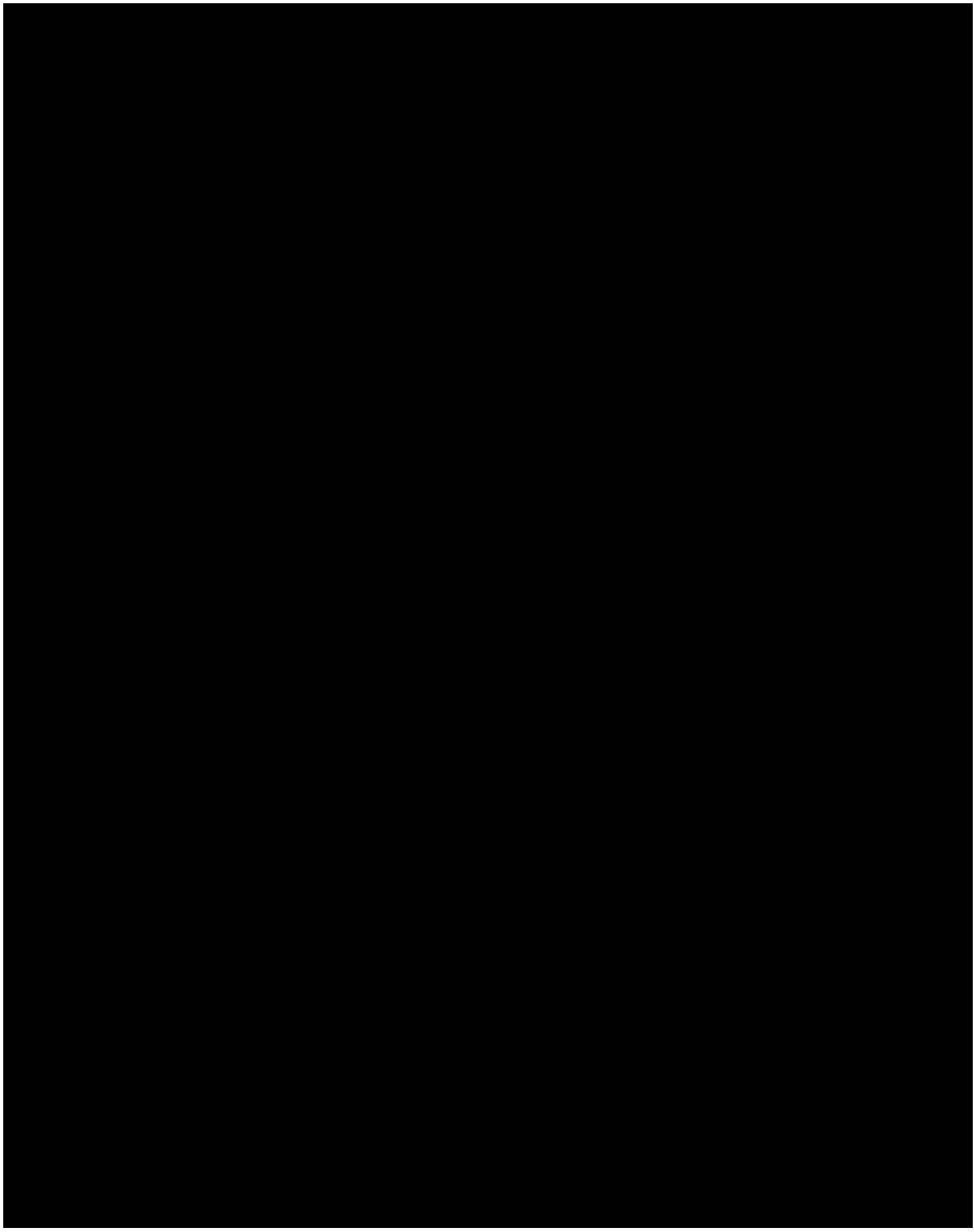
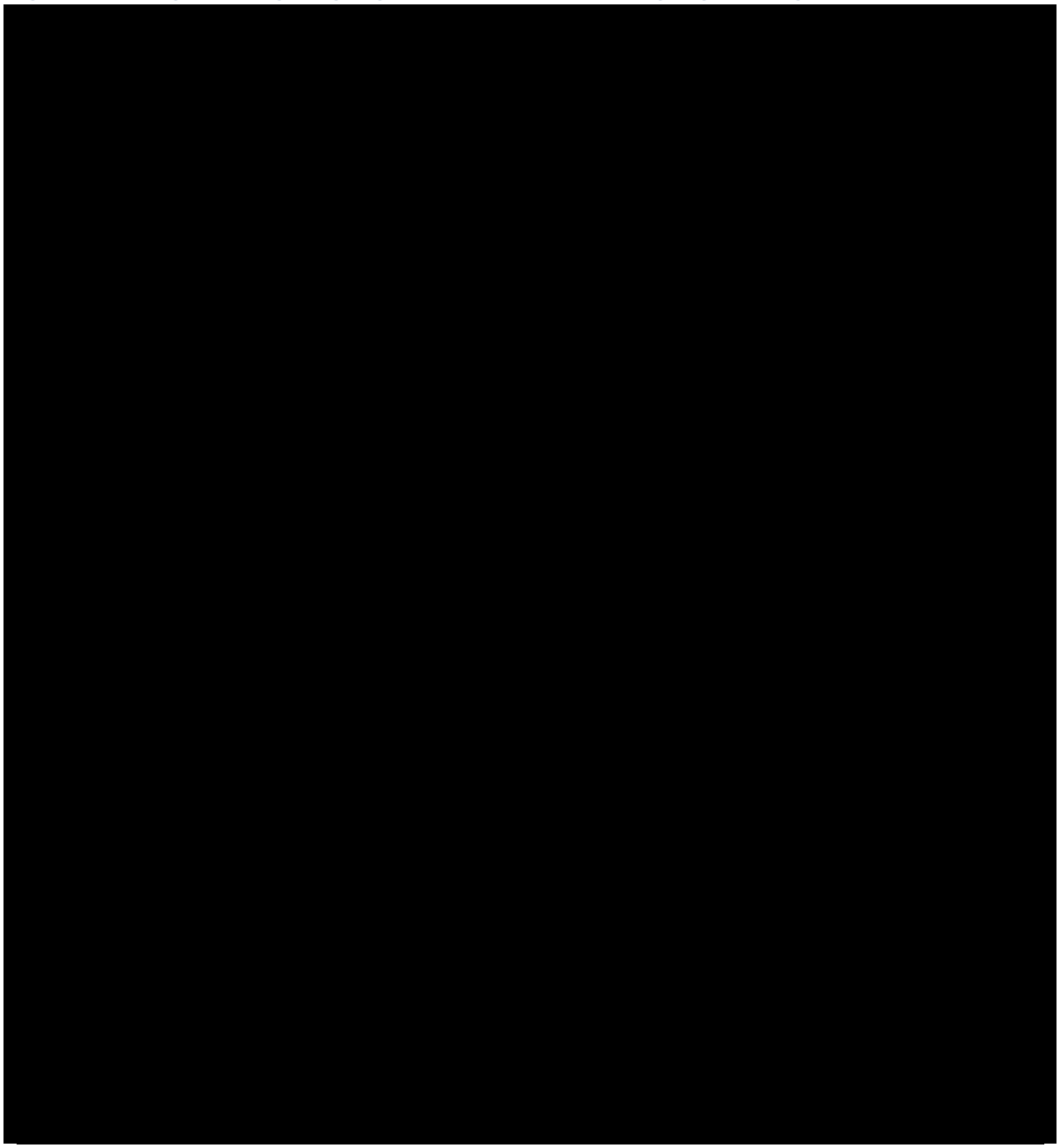


Figure 25: Programming language utilised for PSW using logistic regression



Appendix C: Systematic literature review for selection of prognostic variables

As outlined in response to Question A24e above, an SLR was conducted to inform the appropriate selection of variables which were prognostic to be included in the analysis. The aim of the SLR was to identify studies that provide information on prognostic factors and predictive factors (treatment-effect modifiers) associated with the indications of interest, and that provide evidence to inform the association between response, progression, and survival, in order to support the modelling of progression-free (PFS) and overall survival (OS) from response data collected in the LIBRETTO-001 trial. Full details of the SLR, including the search terms and all results, are presented below.

Search terms

Search strategies used employed in the SLR for prognostic and predictive factors for Embase, PubMed and Cochrane are presented in Table 33, Table 34 and Table 35, respectively.

Table 33. Embase search strategy for prognostic and predictive factors and prediction of progression of survival from response in NSCLC. Search conducted on the 10th September 2019 (SLR2)

Search Number	Search Terms	Hits
Population		
#1 NSCLC in Adults	('non-small cell lung cancer':de,ab,ti OR 'nonsmall cell lung cancer':de,ab,ti OR NSCLC:de,ab,ti OR 'nonsmall-cell lung cancer':de,ab,ti OR 'non-small-cell lung cancer':de,ab,ti OR (('non-small-cell':de,ab,ti OR 'nonsmall-cell':de,ab,ti OR 'non-small cell':de,ab,ti) AND (cancer*:de,ab,ti OR carcinoma*:de,ab,ti OR neoplasm*:de,ab,ti)) OR 'lung adenocarcinoma'/exp OR 'adenocarcinoma of lung':de,ab,ti OR 'lung adenocarcinoma':de,ab,ti OR (lung:de,ab,ti AND ('adenocarcinoma'/exp OR adenocarcinoma:de,ab,ti)) OR (lung:de,ab,ti AND 'squamous cell':de,ab,ti) OR (lung:de,ab,ti AND adenocarcinom*:de,ab,ti) OR (lung:de,ab,ti AND cancer*:de,ab,ti) OR (lung:de,ab,ti AND neoplasm*:de,ab,ti) OR (lung:de,ab,ti AND carcinoma*:de,ab,ti) OR 'non squamous':de,ab,ti OR 'non small cell lung cancer'/exp OR 'bronchial non small cell cancer':de,ab,ti OR 'bronchial nonsmall cell cancer':de,ab,ti OR 'bronchial non small cell carcinoma':de,ab,ti OR 'bronchial nonsmall cell carcinoma':de,ab,ti OR 'non small cell lung cancer':de,ab,ti OR 'nonsmall cell lung cancer':de,ab,ti OR 'lung non small cell cancer':de,ab,ti OR 'lung nonsmall cell cancer':de,ab,ti OR 'lung non small cell carcinoma':de,ab,ti OR 'lung nonsmall call carcinoma':de,ab,ti OR 'non small cell bronchial cancer':de,ab,ti OR 'nonsmall cell bronchial cancer':de,ab,ti OR 'non small cell lung carcinoma':de,ab,ti OR 'nonsmall cell lung carcinoma':de,ab,ti OR 'non small cell pulmonary cancer':de,ab,ti OR 'nonsmall cell pulmonary cancer':de,ab,ti OR 'non small cell pulmonary carcinoma':de,ab,ti OR 'nonsmall cell pulmonary carcinoma':de,ab,ti OR 'pulmonary non small cell cancer':de,ab,ti OR 'pulmonary nonsmall cell cancer':de,ab,ti OR 'pulmonary non small cell carcinoma':de,ab,ti OR 'pulmonary nonsmall cell carcinoma':de,ab,ti) NOT (('juvenile'/exp OR juvenile*:ti OR	527,640

Search Number	Search Terms	Hits
	infant*:ti OR child*:ti OR adolescen*:ti OR teen*:ti OR youth:ti) NOT ('adult'/exp OR adult*:ti OR 'middle age*':ti OR elderly:ti OR 'old age*':ti))	
#2 2L therapy	('second line therapy'/exp OR 'second line therapy':de,ab,ti OR 'second-line':de,ab,ti OR 'second line':de,ab,ti OR '2nd line':de,ab,ti OR relapse:de,ab,ti OR relapsed:de,ab,ti OR refractory:de,ab,ti OR recurrent:de,ab,ti OR resistant:de,ab,ti OR failed:de,ab,ti OR rescue:de,ab,ti OR pretreated:de,ab,ti OR 'pre-treated':de,ab,ti OR 'previously treated':de,ab,ti OR 're-treated':de,ab,ti OR progressive:de,ab,ti)	2,285,769
#3 MTC	'medullary thyroid cancer'/exp OR 'medullary thyroid cancer':de,ab,ti OR 'medullary thyroid carcinoma':de,ab,ti OR ('medullary thyroid':ab,ti AND (cancer*:ab,ti OR carcinoma*:ab,ti OR neoplasm*:ab,ti OR tumour*:ab,ti OR tumor*:ab,ti)) OR 'medullary thyroid neoplasm':de,ab,ti OR 'medullary thyroid tumour':de,ab,ti OR 'medullary thyroid tumor':de,ab,ti	7,153
#4 TC	'thyroid cancer'/exp OR "thyroid cancer":de,ab,ti OR "thyroid carcinoma":de,ab,ti OR (thyroid:ab,ti AND (cancer*:ab,ti OR carcinoma*:ab,ti OR neoplasm*:ab,ti OR tumour*:ab,ti OR tumor*:ab,ti)) OR "thyroid gland cancer":de,ab,ti OR "thyroidal cancer":de,ab,ti OR "thyroidal gland cancer":de,ab,ti	94,978
Outcomes: Survival/response		
#5	('disease free survival'/exp OR 'disease free':de,ab,ti OR response:de,ab,ti OR progression:de,ab,ti OR responder:de,ab,ti OR 'non-responder':de,ab,ti) AND ('overall survival'/exp OR 'overall survival':de,ab,ti)	192,095
Prognostic and predictive studies		
#6	'prognostic assessment'/exp OR 'prognostic assessment':de,ab,ti OR 'prognostic factor':de,ab,ti OR 'prognostic value':de,ab,ti OR 'effect modification':de,ab,ti OR 'effect modif*':de,ab,ti OR predict*:de,ab,ti OR surrogate*:de,ab,ti OR surrogac*:de,ab,ti OR correlation*:de,ab,ti OR correlate*:de,ab,ti OR association*:de,ab,ti OR associated:de,ab,ti OR relationship*:de,ab,ti OR related:de,ab,ti	11,132,375
Study types		
#7	('observational study'/exp OR 'cohort analysis'/exp OR 'retrospective study'/exp OR 'cross-sectional study'/exp OR 'case control study'/exp OR 'longitudinal study'/exp OR 'register'/exp OR 'prospective study'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR nonrandomized:de,ab,ti OR 'non-randomized':de,ab,ti OR nonrandomised:de,ab,ti OR 'non-randomised':de,ab,ti OR 'real world':de,ab,ti OR ((registry NEXT/1 stud*):de,ab,ti) OR ((observational NEXT/1 stud*):de,ab,ti) OR ((cohort NEXT/1 stud*):de,ab,ti) OR ((cohort NEXT/1 analys*):de,ab,ti) OR ((retrospective NEXT/1 stud*):de,ab,ti) OR (('cross sectional' NEXT/1 stud*):de,ab,ti) OR (('case control' NEXT/1 stud*):de,ab,ti) OR ((longitudinal NEXT/1 stud*):de,ab,ti) OR ((prospective NEXT/1 stud*):de,ab,ti) OR ((database NEXT/1 stud*):de,ab,ti) OR 'meta-analysis':de,ab,ti,kw OR 'meta-analyses':de,ab,ti,kw OR metaanalysis:de,ab,ti,kw OR metaanalyses:de,ab,ti,kw OR ((systematic NEXT/1	2,954,698

Search Number	Search Terms	Hits
	review*):de,ab,ti) OR ((systematic NEXT/1 literature NEXT/1 review*):de,ab,ti) OR 'medical record abstraction':de,ab,ti OR 'electronic health record abstraction':de,ab,ti)	
Exclusions		
#8	'animal'/exp NOT 'human'/exp	5,317,042
#9	comment*:ti OR 'letter':it OR 'editorial':it OR 'note':it OR 'short survey':it OR 'conference review':it OR 'nonhuman'/exp OR 'animal experiment'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'animal model'/exp OR 'in vitro study'/exp OR 'in vitro':de,ab,ti OR 'in vitro studies':de,ab,ti OR 'in vitro technique':de,ab,ti OR 'in vitro techniques':de,ab,ti	12,025,380
#10	(([article]/lim OR [article in press]/lim OR [erratum]/lim OR [review]/lim) AND ([9-8-2009]/sd AND [2009-2019]/py)) OR (([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND ([9-8-2017]/sd AND [2017-2019]/py))	10,528,229
Total: Prognostic/surrogate studies for survival		
#11	(#5 AND #6 AND #7) NOT (#8 OR #9)	32,324
TOTAL: Prognostic/surrogate studies for survival by cancer type		
#12 2L NSCLC	#1 AND #2 AND #11	1,838
#13 NSCLC	#1 AND #11	5,922
#14 MTC	#3 AND #11	22
#15 TC	#4 AND #11	265
Total: Prognostic/surrogate studies for survival in cancer type with date limit		
#16 2L NSCLC	#12 AND #10	1,365
#17 NSCLC	#13 AND #10	4,677
#18 MTC	#14 AND #10	19
#19 TC	#15 AND #10	218
Totals (with date limit for NSCLC)		
#20 2L NSCLC + TC	#15 OR #16	1,606

Abbreviations: 2L: second line; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; TC: thyroid cancer.

Table 34. PubMed search strategy for prognostic and predictive factors and prediction of progression and survival from response in NSCLC. Search conducted on the 10th September 2019 (SLR2)

Search Number	Search Terms	Hits
Population		
#1 NSCLC in Adults	("non-small cell lung cancer"[Text Word] OR "nonsmall cell lung cancer"[Text Word] OR NSCLC[Text Word] OR "nonsmall-cell lung cancer"[Text Word] OR "non-small-cell lung cancer"[Text Word] OR (("non-small-cell"[Text Word] OR "nonsmall-cell"[Text Word] OR "non-small cell"[Text Word]) AND (cancer*[Text Word] OR carcinoma*[Text Word] OR neoplasm*[Text Word])) OR "Adenocarcinoma of Lung"[Mesh] OR "adenocarcinoma of lung"[Text Word] OR "lung adenocarcinoma"[Text Word] OR (lung[Text Word] AND ("Adenocarcinoma"[Mesh] OR adenocarcinoma[Text Word])) OR (lung[Text Word] AND "squamous cell"[Text Word]) OR	314,743

Search Number	Search Terms	Hits
	(lung[Text Word] AND adenocarcinom*[Text Word]) OR (lung[Text Word] AND cancer*[Text Word]) OR (lung[Text Word] AND neoplasm*[Text Word]) OR (lung[Text Word] AND carcinoma*[Text Word]) OR "non squamous"[Text Word] OR "Carcinoma, Non-Small-Cell Lung"[Mesh] OR "bronchial non small cell cancer"[Text Word] OR "bronchial nonsmall cell cancer"[Text Word] OR "bronchial non small cell carcinoma"[Text Word] OR "bronchial nonsmall cell carcinoma"[Text Word] OR "non small cell lung cancer"[Text Word] OR "nonsmall cell lung cancer"[Text Word] OR "lung non small cell cancer"[Text Word] OR "lung nonsmall cell cancer"[Text Word] OR "lung non small cell carcinoma"[Text Word] OR "lung nonsmall call carcinoma"[Text Word] OR "non small cell bronchial cancer"[Text Word] OR "nonsmall cell bronchial cancer"[Text Word] OR "non small cell lung carcinoma"[Text Word] OR "nonsmall cell lung carcinoma"[Text Word] OR "non small cell pulmonary cancer"[Text Word] OR "nonsmall cell pulmonary cancer"[Text Word] OR "non small cell pulmonary carcinoma"[Text Word] OR "nonsmall cell pulmonary carcinoma"[Text Word] OR "pulmonary non small cell cancer"[Text Word] OR "pulmonary nonsmall cell cancer"[Text Word] OR "pulmonary non small cell carcinoma"[Text Word] OR "pulmonary nonsmall cell carcinoma"[Text Word]) NOT (("Infant"[Mesh] OR "Child"[Mesh] OR "Adolescent"[Mesh] OR juvenile*[Title] OR infant*[Title] OR child*[Title] OR adolescen*[Title] OR teen*[Title] OR youth[Title]) NOT ("Adult"[Mesh] OR adult*[Title] OR middle age*[Title] OR elderly[Title] OR old age*[Title]))	
#2 2L therapy	("second line therapy"[Text Word] OR "second-line"[Text Word] OR "second line"[Text Word] OR "2nd line"[Text Word] OR relapse[Text Word] OR relapsed[Text Word] OR refractory[Text Word] OR recurrent[Text Word] OR resistant[Text Word] OR failed[Text Word] OR rescue[Text Word] OR pretreated[Text Word] OR "pre-treated"[Text Word] OR "previously treated"[Text Word] OR "re-treated"[Text Word] OR progressive[Text Word])	1,522,559
#3 MTC	"Thyroid cancer, medullary"[Supplementary Concept] OR "medullary thyroid cancer"[Text Word] OR "medullary thyroid carcinoma"[Text Word] OR ("medullary thyroid"[Title/Abstract] AND (cancer*[Title/Abstract] OR carcinoma*[Title/Abstract] OR neoplasm*[Title/Abstract] OR tumour*[Title/Abstract] OR tumor*[Title/Abstract]) OR "medullary thyroid neoplasm"[Text Word] OR "medullary thyroid tumour"[Text Word] OR "medullary thyroid tumor"[Text Word])	5,578
#4 TC	"Thyroid Neoplasms"[Mesh] OR "thyroid cancer"[Text Word] OR "thyroid carcinoma"[Text Word] OR (thyroid[Title/Abstract] AND (cancer*[Title/Abstract] OR carcinoma*[Title/Abstract] OR neoplasm*[Title/Abstract] OR tumour*[Title/Abstract] OR tumor*[Title/Abstract])) OR "thyroid gland cancer"[Text Word] OR "thyroidal cancer"[Text Word] OR "thyroidal gland cancer"[Text Word]	74,296
Outcomes: Survival/response		
#5	("Disease-Free Survival"[Mesh] OR "disease free"[Text Word] OR response[Text Word] OR progression[Text Word] OR responder[Text Word] OR "non-responder"[Text Word]) AND "overall survival"[Text Word]	86,914

Search Number	Search Terms	Hits
Prognostic and predictive studies		
#6	"prognostic assessment"[Text Word] OR "prognostic factor"[Text Word] OR "prognostic value"[Text Word] OR "effect modification"[Text Word] OR effect modif*[Text Word] OR predict*[Text Word] OR surrogate*[Text Word] OR surrogac*[Text Word] OR correlation*[Text Word] OR correlate*[Text Word] OR association*[Text Word] OR associated[Text Word] OR relationship*[Text Word] OR related[Text Word]	8,818,591
Study types		
#7	"Observational Study"[Publication Type] OR "Cohort Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR "Cross-Sectional Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Registries"[Mesh] OR "Prospective Studies"[Mesh] OR "Meta-Analysis"[Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR "Systematic Review"[Publication Type] OR "Systematic Reviews as Topic"[Mesh] OR systematic[sb] OR nonrandomized[Text Word] OR "non-randomized"[Text Word] OR nonrandomised[Text Word] OR "non-randomised"[Text Word] OR "real world"[Text Word] OR registry stud*[Text Word] OR observational stud*[Text Word] OR cohort stud*[Text Word] OR cohort analys*[Text Word] OR retrospective stud*[Text Word] OR cross sectional stud*[Text Word] OR case control stud*[Text Word] OR longitudinal stud*[Text Word] OR prospective stud*[Text Word] OR database stud*[Text Word] OR "meta-analysis"[Text Word] OR "meta-analyses"[Text Word] OR metaanalysis[Text Word] OR metaanalyses[Text Word] OR systematic review*[Text Word] OR systematic literature review*[Text Word] OR "medical record abstraction"[Text Word] OR "electronic health record abstraction"[Text Word]	2,935,502
Exclusions		
#8	"Animals"[Mesh] NOT "Humans"[Mesh]	4,617,346
#9	"Comment"[Publication Type] OR "Letter"[Publication Type] OR "Editorial"[Publication Type] OR "Animal Experimentation"[Mesh] OR "Models, Animal"[Mesh] OR "In Vitro Techniques"[Mesh] OR "in vitro"[Text Word] OR "in vitro studies"[Text Word] OR "in vitro technique"[Text Word] OR "in vitro techniques"[Text Word]	3,807,545
#10	(("Journal Article"[Publication Type] OR "Published Erratum"[Publication Type] OR "Review"[Publication Type]) AND "2009/08/09"[Date - Publication]:"3000"[Date - Publication]) OR (("Meeting Abstract"[Publication Type] OR "Congress"[Publication Type]) AND "2017/08/09"[Date - Publication] : "3000"[Date - Publication])	9,664,322
Total: Prognostic/surrogate studies for survival		
#11	(#5 AND #6 AND #7) NOT (#8 OR #9)	28,469
TOTAL: Prognostic/surrogate studies for survival by cancer type		
#12 2L NSCLC	#1 AND #2 AND #11	875
#13 NSCLC	#1 AND #11	3,527
#14 MTC	#3 AND #11	23
#15 TC	#4 AND #11	205

Search Number	Search Terms	Hits
Total: Prognostic/surrogate studies for survival in cancer type with date limit		
#16 2L NSCLC	#12 AND #10	702
#17 NSCLC	#13 AND #10	2,928
#18 MTC	#14 AND #10	17
#19 TC	#15 AND #10	165
Totals (with date limit for NSCLC)		
#20 2L NSCLC + TC	#15 OR #16	898

Abbreviations: 2L: second line; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; TC: thyroid cancer.

Table 35. Cochrane search strategy for prognostic and predictive factors and prediction of progression and survival from response in NSCLC. Search conducted on the 12th August 2019 (SLR2)

Search Number	Search Terms	Hits
Population		
#1 NSCLC in Adults	MeSH descriptor: [Adenocarcinoma of Lung] explode all trees	74
#2	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	3,779
#3	("non-small cell lung cancer" OR "nonsmall cell lung cancer" OR NSCLC OR "nonsmall-cell lung cancer" OR "non-small-cell lung cancer" OR (("non-small-cell" OR "nonsmall-cell" OR "non-small cell") AND (cancer* OR carcinoma* OR neoplasm*)) OR "adenocarcinoma of lung" OR "lung adenocarcinoma" OR (lung AND "squamous cell") OR (lung AND adenocarcinom*) OR (lung AND cancer*) OR (lung AND neoplasm*) OR (lung AND carcinoma*) OR "non squamous" OR "bronchial non small cell cancer" OR "bronchial nonsmall cell cancer" OR "bronchial non small cell carcinoma" OR "bronchial nonsmall cell carcinoma" OR "non small cell lung cancer" OR "nonsmall cell lung cancer" OR "lung non small cell cancer" OR "lung nonsmall cell cancer" OR "lung non small cell carcinoma" OR "lung nonsmall call carcinoma" OR "non small cell bronchial cancer" OR "nonsmall cell bronchial cancer" OR "non small cell lung carcinoma" OR "nonsmall cell lung carcinoma" OR "non small cell pulmonary cancer" OR "nonsmall cell pulmonary cancer" OR "non small cell pulmonary carcinoma" OR "nonsmall cell pulmonary carcinoma" OR "pulmonary non small cell cancer" OR "pulmonary nonsmall cell cancer" OR "pulmonary non small cell carcinoma" OR "pulmonary nonsmall cell carcinoma")	26,293
#4	MeSH descriptor: [Adenocarcinoma] explode all trees	6,857
#5	(adenocarcinoma)	10,251
#6	#4 OR #5	13,532
#7	(lung)	68,682
#8	#6 AND #7	2,267
#9	#1 OR #2 OR #3 OR #8	26,293
#10	MeSH descriptor: [Infant] explode all trees	15,492
#11	MeSH descriptor: [Child] explode all trees	1,198

Search Number	Search Terms	Hits
#12	MeSH descriptor: [Adolescent] explode all trees	100,701
#13	(juvenile* OR infant* OR child* OR adolescen* OR teen* OR youth):ti	97,121
#14	MeSH descriptor: [Adult] explode all trees	3,380
#15	(adult* OR middle NEXT age* OR elderly OR old NEXT age*):ti	56,710
#16	(#10 OR #11 OR #12 OR #13) NOT (#14 OR #15)	183,692
#17	#9 NOT #16	25,809
#18 2L therapy	("second line therapy" OR "second-line" OR "second line" OR "2nd line" OR relapse OR relapsed OR refractory OR recurrent OR resistant OR failed OR rescue OR pretreated OR "pre-treated" OR "previously treated" OR "re-treated" OR progressive)	151,151
#19 MTC	("medullary thyroid cancer" OR "medullary thyroid carcinoma" OR "medullary thyroid neoplasm" OR "medullary thyroid tumour" OR "medullary thyroid tumor")	140
#20	("medullary thyroid" AND (cancer* OR carcinoma* OR neoplasm* OR tumour* OR tumor*))	144
#21	#19 OR #20	144
#22 TC	MeSH descriptor: [Thyroid Neoplasms] explode all trees	575
#23	("thyroid cancer" OR "thyroid carcinoma" OR "thyroid gland cancer" OR "thyroidal cancer" OR "thyroidal gland cancer")	1,241
#24	(thyroid AND (cancer* OR carcinoma* OR neoplasm* OR tumour* OR tumor*)):ti,ab,kw	2,137
#25	#22 OR #23 OR #24	2,237
Outcomes: Survival/response		
#26	MeSH descriptor: [Disease-Free Survival] explode all trees	6,616
#27	"disease free" OR response OR progression OR responder OR "non-responder"	267,036
#28	#26 OR #27	267,036
#29	("overall survival")	36,375
#30	#28 AND #29	28,246
Prognostic and predictive studies		
#31	("prognostic assessment" OR "prognostic factor" OR "prognostic value" OR "effect modification" OR effect NEXT modif* OR predict* OR surrogate* OR surrogac* OR correlation* OR correlate* OR association* OR associated OR relationship* OR related)	1,587,520
Study types		
#32	MeSH descriptor: [Cohort Studies] explode all trees	143,395
#33	MeSH descriptor: [Retrospective Studies] explode all trees	8,160
#34	MeSH descriptor: [Cross-Sectional Studies] explode all trees	4,726
#35	MeSH descriptor: [Case-Control Studies] explode all trees	12,921
#36	MeSH descriptor: [Longitudinal Studies] explode all trees	6,032
#37	MeSH descriptor: [Registries] explode all trees	910
#38	MeSH descriptor: [Prospective Studies] explode all trees	88,214
#39	MeSH descriptor: [Meta-Analysis as Topic] explode all trees	293

Search Number	Search Terms	Hits
#40	MeSH descriptor: [Systematic Reviews as Topic] explode all trees	12
#41	(nonrandomized OR "non-randomized" OR nonrandomised OR "non-randomised" OR "real world" OR registry NEXT stud* OR observational NEXT stud* OR cohort NEXT stud* OR cohort NEXT analys* OR retrospective NEXT stud* OR cross NEXT sectional NEXT stud* OR case NEXT control NEXT stud* OR longitudinal NEXT stud* OR prospective NEXT stud* OR database NEXT stud* OR "meta-analysis" OR "meta-analyses" OR metaanalysis OR metaanalyses OR systematic NEXT review* OR systematic NEXT literature NEXT review* OR "medical record abstraction" OR "electronic health record abstraction")	249,980
#42	("Observational Study" OR "Meta-Analysis" OR "Systematic Review"):pt	1,581
#43	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42	285,766
Exclusions		
#44	MeSH descriptor: [Animals] explode all trees	15,483
#45	MeSH descriptor: [Humans] explode all trees	8,286
#46	#44 NOT #45	7,197
#47	MeSH descriptor: [Animal Experimentation] explode all trees	4
#48	MeSH descriptor: [Models, Animal] explode all trees	464
#49	MeSH descriptor: [In Vitro Techniques] explode all trees	1,458
#50	("in vitro" OR "in vitro studies" OR "in vitro technique" OR "in vitro techniques")	22,199
#51	(Comment OR Letter OR Editorial):pt	14,237
#52	#47 OR #48 OR #49 OR #50 OR #51	37,062
Total: Prognostic/surrogate studies for survival		
#53	(#30 AND #31 AND #43) NOT (#46 OR #52)	6,803
TOTAL: Prognostic/surrogate studies for survival by cancer type		
#54 2L NSCLC	#17 AND #18 AND #53	554
#55 NSCLC	#17 AND #53	1,176
#56 MTC	#21 AND #53	5
#57 TC	#25 AND #53	31
Total: Prognostic/surrogate studies for survival in cancer type with date limit		
#58 2L NSCLC	#54 AND Publication date from 2009/08/09	459
#59 NSCLC	#55 AND Publication date from 2009/08/09	966
#60 MTC	#56 AND Publication date from 2009/08/09	5
#61 TC	#57 AND Publication date from 2009/08/09	29
Totals (with date limit for NSCLC)		
#62 2L NSCLC + TC	#57 OR #58	478

Abbreviations: 2L: second line; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; TC: thyroid cancer.

Inclusion and exclusion

The inclusion and exclusion criteria are presented in Table 36. The inclusion and exclusion criteria identified the population and disease condition, interventions, comparators, outcomes and study types.

Table 36. Inclusion and Exclusion Criteria for Level 1 Screening in SLR 2: Prognostic and Predictive Factors and Association Between Response, Progression-Free Survival and Overall Survival[a]

Criteria	Included	Excluded
Population	• NSCLC patients on second or subsequent-lines of therapy • Patients with MTC, PTC, or a PTC subgroup of within a study of patients with DTC (any line of therapy)	• Children and adolescents for NSCLC only
Intervention	• No restrictions	• None
Comparators	• No restrictions	• None
Outcomes	To be included in the review, a study must provide relevant data pertaining to one of the following: • Prognostic factors • Predictive factors (treatment-effect modifiers) • Relationship between response and either PFS or OS	• Studies that do not report at least 1 of the outcomes of interest
Study design	• Prospective cohort studies • Longitudinal studies • Prognostic studies • Registry studies • Case-control studies • Cross-sectional surveys • Retrospective studies • Systematic reviews[b] • Meta-analyses • Secondary analyses of RCTs and single-arm trials with outcomes of interest	• Preclinical studies • Phase 1 studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Nonsystematic reviews
Language	• All languages	• None
Date	• NSCLC studies: past 10 years • MTC, PTC and DTC studies: no data limit	• Outside date range

Footnote: [a]If it was unclear whether a study meet any criterion during the level 1 screening process, the study was progressed to full-text screening to confirm its inclusion in the review.
[b]Systematic reviews were included at level 1 screening, used for identification of primary studies, and then excluded at level 2 screening.
Abbreviations: DTC: differentiated thyroid cancer; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; PTC: papillary thyroid cancer; RCT: randomised controlled trial; SLR: systematic literature review.

Results

Electronic Databases

The electronic database searches were performed using the predefined search strategy. The searches were conducted on September 30, 2019, and were not limited by date, except for NSCLC studies, which were limited to articles published after 2009. These searches yielded a total of 3,040 titles (Embase: 1,630; PubMed: 904; Cochrane: 506) of which 594 records were duplicates (Table 37). Therefore, 2,446 titles and/or abstracts were eligible for screening. The titles and abstracts were exported to an Excel document for screening purposes. The titles and abstracts were then reviewed by one researcher, and 10% of them were reviewed independently by another researcher, for inclusion and exclusion.

Table 37. Search results by database

Database	Records	Unique Records
Embase	1,630	1,615
PubMed	904	465
Cochrane	506	366
Totals	**3,040**	**2,446**

Hand searches

Ten articles were identified as authoritative sources that addressed prognostic or predictive factors for non-small cell lung cancer in a first-line treatment setting. These articles are presented in Table 38.

Table 38. Articles identified from hand searches

Ref ID	Reference
HS1	Cai W, Su C, Li X, Fan L, Zheng L, Fei K, et al. KIF5B-RET fusions in Chinese patients with non–small cell lung cancer. Cancer. 2013;119(8):1486-94.
HS2	Cong XF, Yang L, Chen C, Liu Z. KIF5B-RET fusion gene and its correlation with clinicopathological and prognostic features in lung cancer: a meta-analysis. Onco Targets Ther. 2019;12:4533.
HS4	Lee GD, Lee SE, Oh DY, Yu DB, Jeong HM, Kim J, et al. MET exon 14 skipping mutations in lung adenocarcinoma: clinicopathologic implications and prognostic values. J Thorac Oncol. 2017;12(8):1233-46.
HS3	Lee SE, Lee B, Hong M, Song JY, Jung K, Lira ME, et al. Comprehensive analysis of RET and ROS1 rearrangement in lung adenocarcinoma. Mod Pathol. 2015;28(4):468.
HS5	Song Z, Yu X, Zhang Y. Clinicopathologic characteristics, genetic variability and therapeutic options of RET rearrangements patients in lung adenocarcinoma. Lung Cancer. 2016;101:16-21.
HS6	Tsai TH, Wu SG, Hsieh MS, Yu CJ, Yang JCH, Shih JY. Clinical and prognostic implications of RET rearrangements in metastatic lung adenocarcinoma patients with malignant pleural effusion. Lung Cancer. 2015;88(2):208-14.
HS7	Tsuta K, Kohno T, Yoshida A, Shimada Y, Asamura H, Furuta K, et al. RET-rearranged non-small-cell lung carcinoma: a clinicopathological and molecular analysis. Br J Cancer. 2014;110(6):1571.
HS8	Wang R, Hu H, Pan Y, Li Y, Ye T, Li C, et al. RET fusions define a unique molecular and clinicopathologic subtype of non–small-cell lung cancer. J Clin Oncol. 2012;30(35):4352-9.

Ref ID	Reference
HS9	Yu T, Xue S, Jia C, Wang R. KIF5B-RET and EML4-ALK fusion gene expression status and survival analysis of stage IV NSCLC patients. J Pract Oncol. 2018.
HS10	Zheng D, Wang R, Ye T, Yu S, Hu H, Shen X, et al. MET exon 14 skipping defines a unique molecular class of non-small cell lung cancer. Oncotarget. 2016;7(27):41691.

Abbreviations: HS: hand search; Ref ID; reference identifier.

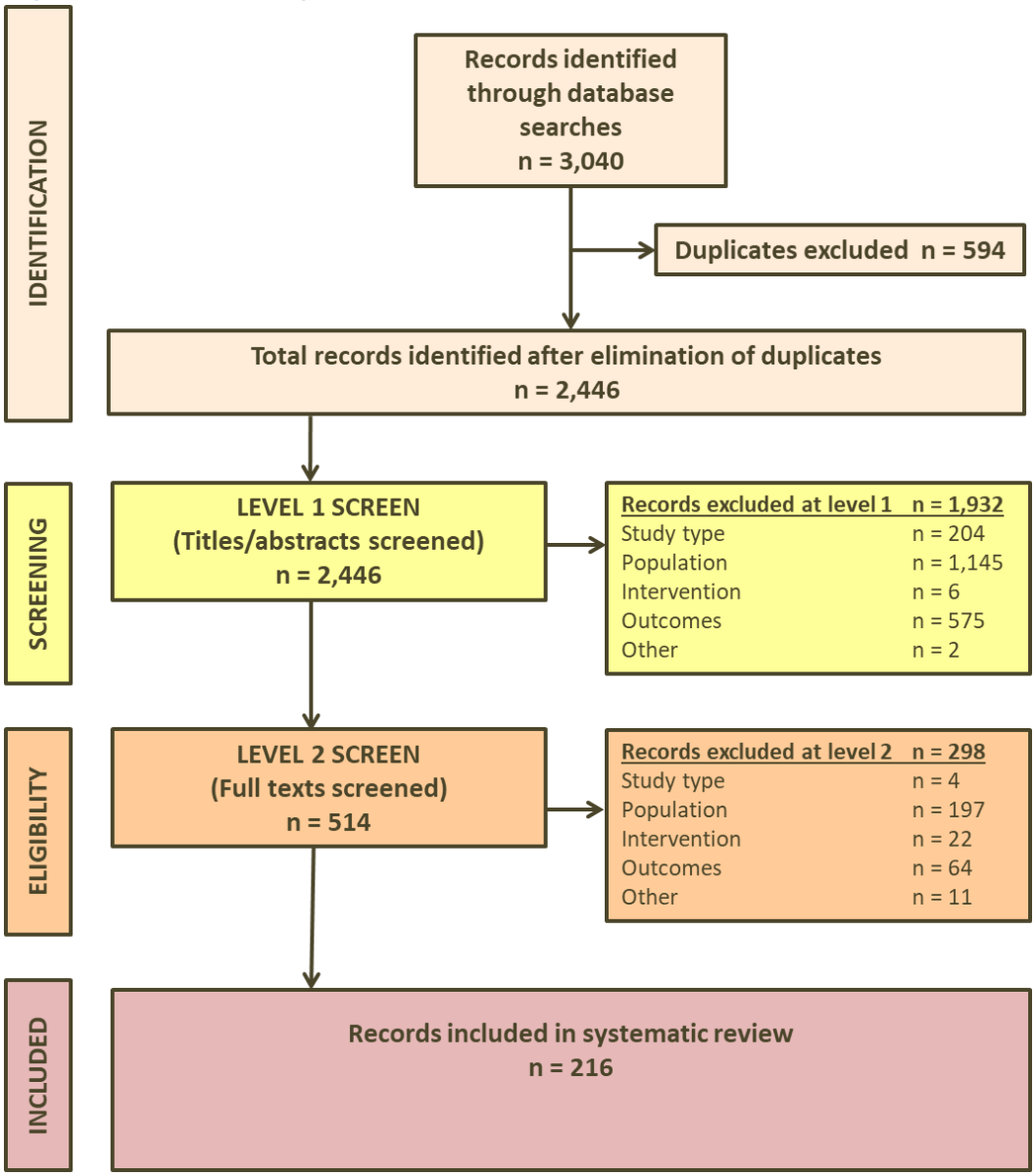
Screening process and results

A total of 2,446 records (titles and abstracts) were selected from databases for manual screening. Titles and abstracts of the studies identified from the searches were reviewed according to predefined inclusion and exclusion criteria presented in the protocol.

After the initial (level 1) screening of titles and abstracts, 514 publications were progressed to further screening (level 2). At the level 2 screening, 216 articles met the predefined inclusion criteria and thus were selected for data extraction.

The volume of studies included and excluded at each stage of screening is shown in the PRISMA diagram (Figure 26). The 216 studies ultimately included in the review are presented in Table 39, and Table 40 presents articles in a foreign language that would require translation prior to data extraction.

Figure 26. PRISMA diagram



Abbreviations: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 39. Articles Included at Level 2 Screening

Study Name/NCT Number/Trial Registration Number/Primary Author (Year)	Primary Ref ID	Primary Reference	Secondary Reference ID	Secondary Reference
Abraham (2011)	1521	Abraham DT, Low TH, Messina M, Jackson N, Gill A, Chou AS, et al. Medullary thyroid carcinoma: Long-term outcomes of surgical treatment. Ann Surg Oncol. 2011;18(1):219-25.		
Acharyya (2012)	1415	Acharyya S, Sau S, Dasgupta P, Chakraborty A, Gangopadhyay S. Skin rash as a surrogate marker of clinical response of targeted therapy using gefitinib in advanced or metastatic non-small-cell lung cancer-a retrospective study. J Indian Med Assoc. 2012;110(7):474-6.		
Agelaki (2010)	2303	Agelaki S, Hatzidaki D, Kotsakis A, Papakotoulas P, Polyzos A, Ziras N, et al. Non-platinum-based first-line followed by platinum-based second-line chemotherapy or the reverse sequence in patients with advanced non-small cell lung cancer: a retrospective analysis by the lung cancer group of the Hellenic Oncology Research Group. Oncology. 2010;78(3-4):229-36.		
Ahmed (2015)	1038	Ahmed RA, Aboelnaga EM. Thyroid cancer in Egypt: histopathological criteria, correlation with survival and oestrogen receptor protein expression. Pathol Oncol Res. 2015;21(3):793-802.		
Alencar (2019)	48	Alencar R, Kendler DB, Andrade F, Nava C, Bulzico D, de Noronha Pessoa CC, et al. CA19-9 as a predictor of worse clinical outcome in medullary thyroid carcinoma. Eur Thyroid J. 2019;8(4):186-91.		
Almutairi (2019)	4	Almutairi AR, Alkhatib N, Martin J, Babiker HM, Garland LL, McBride A, et al. Comparative efficacy and safety of immunotherapies targeting the PD-1/PD-L1 pathway for previously treated advanced non-small cell lung cancer: A Bayesian network meta-analysis. Crit Rev Oncol Hematol. 2019;142:16-25.		
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Study Name/NCT Number/Trial Registration Number/Primary Author (Year)	Primary Ref ID	Primary Reference	Secondary Reference ID	Secondary Reference
Li (2019)	218	Li J, He Q, Yu X, Khan K, Weng X, Guan M. Complete response associated with immune checkpoint inhibitors in advanced non-small-cell lung cancer: A meta-analysis of nine randomized controlled trials. Cancer Manag Res. 2019;11:1623-9.		
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Study Name/NCT Number/Trial Registration Number/Primary Author (Year)	Primary Ref ID	Primary Reference	Secondary Reference ID	Secondary Reference
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Study Name/NCT Number/Trial Registration Number/Primary Author (Year)	Primary Ref ID	Primary Reference	Secondary Reference ID	Secondary Reference
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Study Name/NCT Number/Trial Registration Number/Primary Author (Year)	Primary Ref ID	Primary Reference	Secondary Reference ID	Secondary Reference
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Study Name/NCT Number/Trial Registration Number/Primary Author (Year)	Primary Ref ID	Primary Reference	Secondary Reference ID	Secondary Reference
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Xiao (2015)	1091	Xiao BK, Yang JY, Dong JX, Ji ZS, Si HY, Wang WL, et al. Meta-analysis of seven randomized control trials to assess the efficacy and toxicity of combining EGFR-TKI with chemotherapy for patients with advanced NSCLC who failed first-line treatment. Asian Pac J Cancer Prev. 2015;16(7):2915-21.		
Xing (2018a)	259	Xing P, Mu Y, Wang Y, Hao X, Zhu Y, Hu X, et al. Real world study of the continuation of bevacizumab beyond disease progression after first-line treatment containing bevacizumab in Chinese patients with advanced non-small cell lung cancer. Thorac Cancer. 2018;9(12):1716-24.		

Study Name/NCT Number/Trial Registration Number/Primary Author (Year)	Primary Ref ID	Primary Reference	Secondary Reference ID	Secondary Reference
Xing (2018b)	349	Xing P, Wang Q, Ma D, Hao X, Wang M, Wang Y, et al. Outcomes of ALK-positive non-small-cell lung cancer (NSCLC) patients treated with crizotinib: a multicenter cohort retrospective study. J Thorac Oncol. 2018;13(10):S799.	352	Ma D, Xing P, Wang Q, Hao X, Wang M, Wang Y, et al. Real-world clinical benefit of continuing crizotinib beyond progression disease (CBPD) in patients with advanced ALK-positive NSCLC. J Thorac Oncol. 2018;13(10):S800.
Xu (2016)	2226	Xu H, Minchella K, Zhou D, Al-Huniti N. A meta-analysis of the efficacy of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor treatment in nonsmall-cell lung cancer patients. J Clin Oncol. 2016;34.		
Yamaguchi (2019)	123	Yamaguchi O, Kaira K, Mouri A, Shiono A, Hashimoto K, Miura Y, et al. Re-challenge of afatinib after 1st generation EGFR-TKI failure in patients with previously treated non-small cell lung cancer harboring EGFR mutation. Cancer Chemother Pharmacol. 2019;83(5):817-25.		
Yamauchi (2019)	96	Yamauchi I, Yasoda A, Matsumoto S, Sakamori Y, Kim YH, Nomura M, et al. Incidence, features, and prognosis of immune-related adverse events involving the thyroid gland induced by nivolumab. PLoS One. 2019;14(5).		
Yang (2017)	2069	Yang J, Liang M, Jia Y, Wang L, Lin L, Geng J, et al. Therapeutic response and long-term outcome of differentiated thyroid cancer with pulmonary metastases treated by radioiodine therapy. Oncotarget. 2017;8(54):92715-26.		
Younes (2011)	1467	Younes RN, Pereira JR, Fares AL, Gross JL. Chemotherapy beyond first-line in stage IV metastatic non-small cell lung cancer. Rev Assoc Med Bras. 2011;57(6):686-91.		
Yuksel (2019)	131	Yuksel U, Turanli S, Acar Y, Berberoglu U. The prognostic factors for clinical N1b patients in thyroid papillary carcinoma. J Cancer Res Ther. 2019;15(3):681-5.		

Study Name/NCT Number/Trial Registration Number/Primary Author (Year)	Primary Ref ID	Primary Reference	Secondary Reference ID	Secondary Reference
Zeng (2014)	2333	Zeng Z, Yan HH, Zhang XC, Zhong WZ, He YY, Guan JL, et al. Reduced chemotherapy sensitivity in EGFR-mutant lung cancer patient with frontline EGFR tyrosine kinase inhibitor. Lung Cancer. 2014;86(2):219-24.		
Zhang (2012)	1375	Zhang J, Huang Y, Li X, Guo Y, Zhao Y, Xue C, et al. The impact of tumor size change after target therapy on survival: Analysis of patients enrolled onto three clinical trials of advanced NSCLC from one institution. Onco Targets Ther. 2012;5:349-55	912	He X, Zhang Y, Ma Y, Zhou T, Zhang J, Hong S, et al. Optimal tumor shrinkage predicts long-term outcome in advanced nonsmall cell lung cancer (NSCLC) treated with target therapy: Result from 3 clinical trials of advanced NSCLC by 1 institution. Medicine. 2016;95(31).
Zhang (2019)	110	Zhang S, Pease DF, Joshi S, Wang Y, Patel M. Clinical predictors of efficacy for immune checkpoint inhibition in lung cancer patients. J Clin Oncol. 2019;37:e20600.		
Zhang (2018)	303	Zhang XY, Song HJ, Qiu ZL, Shen CT, Chen XY, Sun ZK, et al. Pulmonary metastases in children and adolescents with papillary thyroid cancer in China: prognostic factors and outcomes from treatment with 131 I. Endocrine. 2018;62(1):149-58.		
Zhang (2009a)	1596	Zhang YF, Chen ZW, Lu S. Pemetrexed monotherapy versus pemetrexed plus platinum combination as second-line treatment for advanced non-small cell lung cancer. Chin Med J. 2009;122(20):2472-6.		
Zhang (2009b)	1605	Zhang YF, Yu YF, Lu S. Comparison of single-agent docetaxel versus docetaxel plus platinum combination agent in second-line treatment for advanced non-small cell lung cancer. Zhonghua Yi Xue Za Zhi (Taipei). 2009;89(22):1544-8.		

Study Name/NCT Number/Trial Registration Number/Primary Author (Year)	Primary Ref ID	Primary Reference	Secondary Reference ID	Secondary Reference
Zhao (2015)	2213	Zhao L, Li W, Zhang H, Hou N, Guo L, Gao Q. Angiogenesis inhibitors rechallenge in patients with advanced non-small-cell lung cancer: a pooled analysis of randomized controlled trials. Onco Targets Ther. 2015;8:2775-81.		
Zhao (2019)	75	Zhao S, Zhang Z, Zhang Y, Hong S, Zhou T, Yang Y, et al. Progression-free survival and one-year milestone survival as surrogates for overall survival in previously treated advanced non-small cell lung cancer. Int J Cancer. 2019;144(11):2854-66.		
Zheng (2014)	1231	Zheng L, Wang WX, Shao L, Song ZB, Zhang YP. Efficacy and safety of icotinib in 299 patients with advanced non-small cell lung cancer after failure of chemotherapy. TUMOR. 2014;34(7):629-35.		
Zheng (2017)	812	Zheng Z, Jin X, Lin B, Su H, Chen H, Fei S, et al. Efficacy of second-line tyrosine kinase inhibitors in the treatment of metastatic advanced non-small-cell lung cancer harboring exon 19 and 21 EGFR mutations. J Cancer. 2017;8(4):597-605.		
Zhou (2019)	241	Zhou T, Wu C, Zhang C, Li P, Dong H, Zhou X, et al. A retrospective study of low-dose apatinib combined with S-1 in patients with advanced non-small cell lung cancer. J Thorac Dis. 2019;11(5):1831-7.	115	Zhou T, Zhou X, Li P, Wu C, Zhang C, Dong H, et al. A retrospective study of low-dose apatinib combined with S-1 in patients with advanced non-small cell lung cancer. J Clin Oncol. 2019;37:e20666.
Zietemann (2011)	1489	Zietemann V, Duell T. Prevalence and effectiveness of first-, second-, and third-line systemic therapy in a cohort of unselected patients with advanced non-small cell lung cancer. Lung Cancer. 2011;73(1):70-7.		
Zugazagoitia (2013)	1349	Zugazagoitia J, Puente J, González-Larriba JL, Manzano A, Sotelo M, Hernández S, et al. Erlotinib versus pemetrexed for pretreated non-squamous non-small cell lung cancer patients in clinical practice. Oncology (Switzerland). 2013;84(5):255-64.		

Abbreviations: NCT: national clinical trial; Ref ID: reference identifier.

Table 40. Foreign language articles of interest included at Level 2 screening

Ref ID	Reference
1637	Bacha S, Cherif H, Habibech S, Sghaier A, Cheikhrouhou S, Racil H, et al. Prognostic factors for second-line chemotherapy of metastatic non-small-cell lung cancer. Tunis Med. 2017;95(8-9):772-6.
391	Chen L, Zhao P, Cao K, Jin L, Xu R, Tang X. Efficacy and safety of immune checkpoint inhibitors in the treatment of non-small cell lung cancer: A meta-analysis. TUMOR. 2018;38(8):780-91.
200	Laktionov KK, Arzumanyan AL, Bolotina LV, Breder VV, Buevich NN, Danilova AS, et al. Efficacy of nivolumab (Nivo) during 2+ line treatment and quality of life in patients with advanced refractory non-small cell lung cancer: Interim results of prospective observational study. Vopr Onkol. 2019;65(1):99-105.
373	Shimabukuro I, Noguchi S, Uyama K, Torii R, Ishimoto H, Yoshii C, et al. Efficacy and safety of carboplatin/nanoparticle albumin-bound paditaxel combination chemotherapy in patients with advanced non-small-cell lung cancer or recurrent non-small-cell lung cancer following surgery. Gan To Kagaku Ryoho. 2018;45(9):1305-10.

Identified prognostic factors

The identified prognostic and predictive factors in NSCLC are presented in Table 41.

Table 41. Prognostic and predictive factors in NSCLC

Prognostic Factor	Details	Source
Age	Younger age is associated with better prognosis	Martin et al. (2017) Mo et al. (2016) Chang et al. (2017a) Minami et al. (2017) Sau et al. (2013) Younes et al. (2011) Zietemann and Duell (2011) Bacha et al. (2017) Choi et al. (2015) Lee et al. (2016)
	Older age is associated with better prognosis	Reinmuth et al. (2013) Stroh et al. (2016) Pan et al. (2013) Tsao et al. (2012) Sheikh and Chambers (2013)[a]
	Older women (aged 65 or 70 and above) had more grade 3 to 4 nonhematologic toxicities, worse PFS (except those treated with erlotinib-bexarotene), higher DCR	Tsao et al. (2012)
Sex	Being male was associated with better prognosis	Minami et al. (2017)
	Being female was associated with better prognosis	Chang et al. (2017a) Mo et al. (2016)

		Milella et al. (2012) Younes et al. (2011)[a] Garassino et al. (2018) Paramanathan et al. (2013)[a] Cioffi et al. (2013) Choi et al. (2015) Kim et al. (2010b)[a] Chang et al. (2010) Lie et al. (2011) Scartozzi et al. (2010) Sim et al. (2018) (Kris 2003 IDEAL II)
	Gender was a predictor of better prognostics	Sim et al. (2018) (Fukuoka 2003 IDEAL I) Zheng et al. (2014)[a] Sau et al. (2013)[a]
Weight/BMI	Weight loss/negative BMI change/lower weight or BMI was associated with worse prognostics	Kollipara et al. (2019) Rančić et al. (2014) Rančić et al. (2014) Aydiner et al. (2013) Minami et al. (2017) Laktionov et al. (2018)[a] Leroy et al. (2017)[a] Zietemann and Duell (2011) Dumenil et al. (2018)[a] Dumenil et al. (2018)[a]
	BMI was a predictor of response	Sim et al. (2018) (Fukuoka 2003 IDEAL I)
Performance status	Patients with lower ECOG scores had prolonged OS	Leng et al. (2019) Kim et al. (2019)

		Buttigliero et al. (2019) Peruzzo et al. (2019) Yamaguchi et al. (2019) Montana et al. (2019)[a] Garde-Noguera et al. (2018) Laktionov et al. (2018)[a] Lee et al. (2018) Martin et al. (2017) Leroy et al. (2017)[a] Minami et al. (2017) Zheng et al. (2017) Tatli et al. (2015) Cao et al. (2014) Liu et al. (2014) Rančić et al. (2014) Pan et al. (2013) Cioffi et al. (2013) Aydiner et al. (2013) Inal et al. (2012) Lie et al. (2011) Chang et al. (2010) Choi et al. (2015) Ludovini et al. (2011) Song et al. (2011) Vasile et al. (2015)[a] Kuo et al. (2014)[a] Kim et al. (2010b)

		Cheon et al. (2011) Sheikh and Chambers (2013) Kuo et al. (2014)[b] Paramanathan et al. (2013) Lu et al. (2012) Younes et al. (2011) Garassino et al. (2018) Igawa et al. (2019) Choi et al. (2015) Dumenil et al. (2018)[a] Scartozzi et al. (2010) Inal et al. (2012) Zhang et al. (2009a) Zhang et al. (2009b) Zheng et al. (2014) Sau et al. (2013)
	Patients with lower ECOG scores had prolonged PFS	Kim et al. (2019) Yamaguchi et al. (2019) Tamiya et al. (2018) Laktionov et al. (2018)[a] Fujimoto et al. (2018) Naoki et al. (2017) Zheng et al. (2017) Oya et al. (2017) Chang et al. (2016) Minami et al. (2015) Liu et al. (2014)

		Rančić et al. (2014) Pan et al. (2013) Cioffi et al. (2013) Inal et al. (2012) Kim et al. (2010a)[a] Dumenil et al. (2018) Song et al. (2011)[a] Shukuya et al. (2016) Inal et al. (2012) Zheng et al. (2014)[a] Dumenil et al. (2018) Ludovini et al. (2011)
	PS at the end of second-line treatment and at the start of second and third-line treatmenta were independent prognosticators for post-progression survival	Kotake et al. (2017)
	PS (Karnofsky) of less than 90 at diagnosis was a significant predictor for no DC and OS after first- and third line therapy, poor PFS after first-line therapy	Zietemann and Duell (2011)
	Better ECOG performance was associated with disease stabilization with gefitinib	Lie et al. (2011)
	PS independently predicted a higher DCR	Kim et al. (2010a)
	PS was associated with favourable response	Chang et al. (2017b) Cioffi et al. (2013) Ludovini et al. (2011) Sim et al. (2018) (Fukuoka 2003 IDEAL I) Kuo et al. (2014)[b]
Smoking status	Having never smoked is an independent predictor of better PFS	Buttigliero et al. (2019) Yamaguchi et al. (2019) Milella et al. (2012)

		Cioffi et al. (2013) Song et al. (2011)[a]
	Having never smoked is an independent predictor of better OS	Buttigliero et al. (2019) Zhao et al. (2019)[a] Jin et al. (2018) Zheng et al. (2017) Cao et al. (2014) Sheikh and Chambers (2013)[a] Lie et al. (2011)[a] Pan et al. (2013) Cioffi et al. (2013) Aydiner et al. (2013)[a] Chang et al. (2010) Choi et al. (2015)[a] Kim et al. (2010b)[a] Paramanathan et al. (2013)[a] Zhang et al. (2012)[a] Reinmuth et al. (2013)
	Having never smoked was significantly associated with poor PFS	Tamiya et al. (2018) Fujimoto et al. (2018) Kim et al. (2017a) Oya et al. (2017)
	Being a non-smoker was associated with response	Cioffi et al. (2013) Ludovini et al. (2011)
	Smoking habits were considered an independent prognostic factor for OS	Sau et al. (2013) Zhang et al. (2012)
	Being a non-smoker was associated with disease stabilisation with gefitinib	Lie et al. (2011)

	Smoking history was reported to be a significant prognostic factor (Scagliotti, 2009), was a prognostic factor in patients with non-squamous NSCLC (Syrigos, 2010) and for survival after progression in previously treated patients (Teramukai, 2007)	Mitchell et al. (2012)
Stage at initial diagnosis	Early stage at diagnosis was significantly associated with OS	Leroy et al. (2017) Scartozzi et al. (2010) Igawa et al. (2019)
	Clinical stage influenced the prognosis of NSCLC	Zhang et al. (2009a)[a]
	Stage was associated with PFS	Vasile et al. (2015)[a] Zheng et al. (2014)[a]
	Advanced clinical stage was an independent negative predictive factor of response to CT	Zheng et al. (2014)
	Baseline lung cancer subscale predicted response (Fukuoka 2003 IDEAL I)	Sim et al. (2018)
Time since initial diagnosis	Number of cycles and delay since first-line therapy was significantly associated with OS	Leroy et al. (2017)[a]
Prior therapy	CR/PR/SD to prior therapy is an independent predictor of better survival outcomes	Buttigliero et al. (2019) Cao et al. (2014) Reinmuth et al. (2013) Sheikh and Chambers (2013)
	PR to first-line systemic therapy, which directly reflects the number of first-line–therapy cycles	Dusselier et al. (2019)
	PD as BOR in the first 3 lines of treatment was significantly associated with OS	Leroy et al. (2017)
	Best DC to previous therapy was associated with improved survival performing third-line therapy	Reinmuth et al. (2013)

	In first-line treatment setting, ICIs tended to improve PFS in patients with smoking history. For never-smokers with advanced NSCLC, CT was significantly associated with improvement of PFS. In more than second-line setting, ICIs significantly prolonged OS over that with CT in ever-smokers. For never-smokers with NSCLC, however, ICIs failed to significantly improve OS	Kim et al. (2017b)
	More than 10 months on 1st TKI is independent prognostic factors predicting a better PFS and OS	Yamaguchi et al. (2019)
	The time interval between the two EGFR TKIs equal to or more than 7 months was a statistically significant factors associated with ORR and PFS of EGFR TKI retreatment	Chang et al. (2017b)
	Patients who achieved DC in prior (second-line) treatment had better outcomes than those with disease progression	Tatli et al. (2015)
	Continuation of EGFR-TKI in addition to CT after first-line EGFR-TKI resistance led to shorter OS. However, combination therapy with EGFR-TKI and CT after failure of first-line CT significantly improved the ORR, PFS and OS, clinical benefit being restricted to combining EGFR-TKI with pemetrexed, but not docetaxel	Xiao et al. (2015)
	One regimen of CT (rather than two or three) was associated with significantly longer PFS	Shao et al. (2014)
	Shorter interval between first- and second-line CT for the second line	Minami et al. (2017)
	Time since first-line CT regimen is associated with better PFS and OS c	Rančić et al. (2014)
	Time since first-line therapy response is associated with better PFS and OS	Rančić et al. (2014)[a]
	Time since the previous line of treatment being <6 months is associated with better PFS and OS.	Garde-Noguera et al. (2018)
	Longer PFS of previous CT (≥4 months) was associated with prolonged OS	Lee et al. (2018)

	Absence of grade ≥ 3 AEs during first-line therapy was significantly associated with OS	Leroy et al. (2017)
	Patients who were previously exposed to platinum-based CT as part of CRT had significantly worse OSa, PFS response and clinical benefit ratea	Paramanathan et al. (2013)
	2 or more prior regimens was associated with decreased OS	Aydiner et al. (2013) Kim et al. (2010b)[a]
	Response to second-line CT was an independent prognostic factor for PFS and OS	Inal et al. (2012)
	Response to first-line CT was an independent prognostic factor for OS	Inal et al. (2012) Younes et al. (2011)
	Second-line treatments were independent prognostic factors for survival and OS	Sau et al. (2013)
	PFS after first-line therapy were considered independent prognostic factors for survivala and OS after second-line treatment	Sau et al. (2013)
	Patients that achieved PR following first-line CT had longer median survival after 2nd and/or 3rd line CT compared with patients with no OR, or PD	Younes et al. (2011)
	Receiving any CT was associated with better OS	Younes et al. (2011)[a]
	Receiving any second-line CT was an independent predictor of OS	Younes et al. (2011)
	Patients who achieved PR while receiving gefitinib therapy showed significantly longer OS	Asami et al. (2011)
	Patients with TTPs of less than 12 months with gefitinib therapy were found to have significantly longer OS than patients with TTPs of 12 months or more	Asami et al. (2011)
	The difference in OS between patients undergoing second-line treatment compared with those undergoing first-line treatment preceding CT was significant	Lie et al. (2011)
	Response to second-line treatment influenced the prognosis of NSCLC	Zhang et al. (2009a)[a]

		Zhang et al. (2009b)
	Radiotherapeutic history influenced the prognosis of NSCLC (survival)	Zhang et al. (2009b)[a]
	Median OS of patients who received fourth- or further-line therapy was longer than that of patients who received third- or lesser-line therapy	Choi et al. (2015)
	DC after first-line CT demonstrated longer OS after fourth- or further-line therapy	Choi et al. (2015)[a]
	Number of prior lines was significantly associated with PD on nivolumab	Dumenil et al. (2018)[a]
	Number of prior lines was significantly associated with worse PFS on nivolumab	Dumenil et al. (2018)
	Number of prior lines was an independent predictor of PFS	Igawa et al. (2019)
	2 or more prior CT regimens was associated with decreased PFS	Kim et al. (2010b)
	Response to second-line therapy was a significant predictor of better OS and median TTP in the third-line setting	Scartozzi et al. (2010)
	Prior radiotherapy and immuno/hormonal therapy were predictors of response	Sim et al. (2018) (Fukuoka 2003 IDEAL I)
	TTP to 1st TKI therapy for ≥18 months conferred a longer PFS for afatinib or erlotinib as 2nd TKI therapy	Lee et al. (2016)
	There was a statistically significant difference in the RR (CR+PR) of the study group (patients treated with first-line EGFR-TKI followed by CT) compared with that of the control group (patients treated with inverse sequence)	Zheng et al. (2014)
	Previous TKI treatment was an independent negative predictive factor of response to CT	Zheng et al. (2014)
	DCR and PFS was significantly higher in EGFR-mutant patients treated with inverse sequence compared to patients treated with first-line EGFR-TKI followed by CT	Zheng et al. (2014)
	Regimens of CT (platinum-based or single-agent) was correlated to PFS	Zheng et al. (2014)[a]
	Frontline EGFR-TKI treatment had a higher risk of disease progression	Zheng et al. (2014)

	OS was significantly longer in EGFR-mutant patients treated with inverse sequencing vs treated with first-line EGFR-TKI followed by CT	Zheng et al. (2014)
	Front-line EGFR-TKI treatment was an independent prognostic factor of OS	Zheng et al. (2014)
	2nd-line CT was significant for PFS and OS	Chung et al. (2015)
	Response to first-line TKI treatment was associated with better OS	Kuo et al. (2014)[a]
	Double responders to overall treatment versus single responders and non-responders was associated with better OS	Kuo et al. (2014)[b]
	Shorter PFS with first-line TKI predicted lower RR to second-line CT	Kuo et al. (2014)[b]
	Upfront CT and response after first line CT were significant prognostic factors of OS after second-line therapy	Sau et al. (2013)[a]
Type of prior systemic therapy	Patients who received first-line crizotinib, continued crizotinib beyond PD and received next-generation ALKis after rizotinib failure were associated with improved survival both from crizotinib progression and from the first crizotinib dose	Xing et al. (2018)
	The use of crizotinib is associated positively with OS	Jin et al. (2018)
	Erlotinib was independently associated with a poorer 1-year PFS than gefitinib	Chang et al. (2017a)
	Second-line PST is an independent predictor of worse OS	Peruzzo et al. (2019)
	Platinum-free therapy were significant predictors of no DC after first-line therapy	Zietemann and Duell (2011)
	Use of systemic CS was significantly associated with PDa, lower PFS and OSs on nivolumab	Dumenil et al. (2018)
	The risk of being a non-responder was higher for patients treated with first-line non-platinum-based CT	Agelaki et al. (2010)
	Significantly higher RRs were achieved with first-line platinum-based compared to non-platinum-based CT in patients with better PS and squamous carcinomas	Agelaki et al. (2010)

	Median TTP was significantly shorter for patients receiving first-line non-platinum- based CT and better a PS	Agelaki et al. (2010)
	The risk of death in the first year was significantly higher for patients treated with first-line non-platinum-containing CT	Agelaki et al. (2010)
	Patients included in the 24-week progression-free analysis treated with prior CT had favourable OS	Shukuya et al. (2016)
Prior cancer-related surgery	Patients who had previously received pulmonary surgery exhibited a more favourable prognosis	Chang et al. (2017a) Naoki et al. (2017)[a]
	Surgery history had significant effects on survival	Zhang et al. (2009a) Zhang et al. (2009b)
Metastatic disease	More than one metastatic location is associated with worse PFS and OS	Garde-Noguera et al. (2018) Rančić et al. (2014)[a]
	No brain metastasis was associated with prolonged OS	Lee et al. (2018) Zheng et al. (2017) Fukui et al. (2019)[a] Igawa et al. (2019)
	No brain metastasis was associated with prolonged PFS	Naoki et al. (2017)[a]
	Distant metastasis (M1a) was associated with longer survival	Liu et al. (2014)[a]
	Bone invasion at diagnosis is associated negatively with OS	Jin et al. (2018) Cao et al. (2014)
	Liver invasion/metastasis at diagnosis is associated negatively with OS	Jin et al. (2018) Cao et al. (2014)
	'Other' (classified as not bone, brain, other lung lesions into lung, adrenal, or liver) and no metastatic sites at diagnosis were associated with improved OS and PFS	Pan et al. (2013)

	The presence of intra-abdominal metastasis resulted in decreased OS	Aydiner et al. (2013) Kim et al. (2010b)[a]
	The presence of intra-abdominal metastasis was associated with decreased PFS	Kim et al. (2010b)
	The presence of adrenal gland metastases and involvement of new metastases after first line therapy were significant predictors of no DC after previous therapy	Zietemann and Duell (2011)
	The development of new metastases after first line therapy was a prognostic factor in PFS following second-line therapy	Zietemann and Duell (2011)
	The presence of adrenal gland and bone metastases were predictors of poor OS and presence of adrenal gland, brain and liver metastases were predictors of poor PFS after first-line therapy	Zietemann and Duell (2011)
	Lymph node involvement was significantly associated with poor OS	Bacha et al. (2017)
	Primary metastatic disease and presence of brain metastasis at the initiation of first-line therapy were associated with poor OS	Choi et al. (2015)[a]
	The presence of symptomatic brain metastases was significantly associated with PD on nivolumab	Dumenil et al. (2018)[a]
	The presence of symptomatic CNS metastases was significantly associated with lower OS on nivolumab	Dumenil et al. (2018)
	Absence of pleural metastasis was an independent predictor of the response to first-line TKI treatment	Kuo et al. (2014)[b]
Disease progression at prior lines of therapy	PFS and OS were shorter in rapid rate of progression in the prior line of therapy	Prasanna et al. (2019)
	Time-to-progression > 12 months was associated with longer OS	Mo et al. (2016)
	Progression within 3-6 months (rather than 3 months) following first-line therapy was associated with longer OS	Cao et al. (2014)
	Disease progression at the first tumour evaluation was associated with shorter PFS and OS	Laktionov et al. (2018)

	Number of regimens after progression beyond second-line CT was an independent prognosticator for post-progression survival	Kotake et al. (2017)
	Non-PD in second-line therapy was independent prognosticator for post-progression survival	Kotake et al. (2017)[a]
	Disease progression, when it occurred, significantly lowered OS	Pan et al. (2013)
	Non-responders (progression or tumour stability at the end of the first line of CT versus PR) was significantly associated with poor OS	Bacha et al. (2017)[a]
	Recurrent disease was an independently associated with favourable OS	Choi et al. (2015)
	Time to recurrence ≥12 months was influential on OS	Moro-Sibilot et al. (2015)
	Patients who were progression-free at week 8, week 16 and week 24 had favourable OS	Shukuya et al. (2016)
Comorbidities	Lower SCS was associated with prolonged OS	Lee et al. (2018)
	Having comorbidities were associated with shorter PFS and OS	Rančić et al. (2014) Pan et al. (2013)
	Pre-existing comorbid fatigue and neurology-related concurrent comorbidity was associated with shorter OS	Pan et al. (2013)
	Pre-existing cardiovascular comorbidities were associated with shorter PFS	Pan et al. (2013)
	Diabetes mellitus was a significant prognostic factor for PFS	Inal et al. (2012)
Driver mutations	Presence of a targetable mutation (EGFR, ALK and ROS1) remained significant predictors of PFS and OS	Prasanna et al. (2019)
	EGFR mutation/ALK rearrangement are identified as independent negative predictors of PFS.	Fujimoto et al. (2018) Zheng et al. (2014)[a]
	Mutation positive EGFR status is an independent predictor of better survival outcomes	Buttigliero et al. (2019) Peruzzo et al. (2019) Ludovini et al. (2011)

		Igawa et al. (2019)
	Tendency towards worse OS in patients with KRAS mutations or no identifiable mutation	Peruzzo et al. (2019)
	Absence of KRAS mutation was an independent predictor of longer PFS and OS	Milella et al. (2012)
	The presence of KRAS mutation was significantly associated with lack of response to TKIs treatment	Ludovini et al. (2011)
	EGFR mutation negativity was associated with significantly longer PFS	Kim et al. (2017a) Shao et al. (2014) Chang et al. (2017a) Chang et al. (2016)
	Females with exon 21 mutation had significantly longer retreatment EGFR-TKI PFS	Chang et al. (2017b)
	EGFR exon 19 deletion was significantly associated with prolonged PFS	Naoki et al. (2017) Zheng et al. (2017)
	EGFR exon 19 deletion was significantly associated with prolonged OS	Zheng et al. (2017)
	ORR was higher for EGFR mutation-positive patients with gefitinib	Lee et al. (2012)[c]
	EGFR mutation-positive showed a strong association with PFS with gefitinib	Lee et al. (2012)[c]
	Low pAKT expression was an independent predictor of better DCR, longer PFS and longer OS	Milella et al. (2012)
	HER-2 overexpression was an independent predictor of shorter PFS and OS	Milella et al. (2012)
	pAKT overexpression was an independent predictor of shorter PFS and OS	Milella et al. (2012)
	PD-L1 expression, ≥50% vs. 0-49% was significantly associated with OS	Fukui et al. (2019)
	The RR between patients with exon 19 deletion (higher) and L858R mutation was significantly different	Igawa et al. (2019)

	Median PFS and OS in the exon 19 deletion group was significantly better than the L858R mutation group	Igawa et al. (2019)
	EGFR genotype was an independent predictor of PFS and OS	Igawa et al. (2019)
	The presence of EGFR mutation was significantly associated with objective response to TKIs treatment	Ludovini et al. (2011)
	The presence of KRAS mutation was significantly associated with lack of response to TKIs treatment	Ludovini et al. (2011)
	Patients with mutant PIK3CA was associated with a significantly shorter OS	Ludovini et al. (2011)
	TTP was significantly shorter in patients with mutated PIK3CA and KRAS	Ludovini et al. (2011)
	Patients with EGFR mutation were significantly associated with longer TTP	Ludovini et al. (2011)
	EGFR mutation was an independent predictive factor of favourable response to EGFR-TKIs	Ludovini et al. (2011)
	PIK3CA mutation was a statistically significant predictor of worse OS	Ludovini et al. (2011)
	Median PFS and OS was significantly increased in patients with tissue rebiopsy as the discovery test of T790M compared with patients with liquid biopsy	Auliac et al. (2019)[b]
	EGFR mutation with L858R was significant for PFS and OS	Chung et al. (2015)
	EGFR mutation as exon 19 deletion was associated with response to second-line CT	Kuo et al. (2014)[b]
	L858R mutation tumour was associated with lower response rate in second-line CT	Kuo et al. (2014)[b]
Histology	ADC is an independent predictor of better survival outcomes	Buttigliero et al. (2019) Cheon et al. (2011) Lie et al. (2011) Song et al. (2011) Sheikh and Chambers (2013)[a] Zietemann and Duell (2011)

	Patients with PD during or within 9 months of initiation of first-line platinum-based CT had a significantly worse survival after initiation of second-line treatment, particularly patients with ADC	Reinmuth et al. (2013)
	Non-squamous histology is a predictor of better survival outcomes	Dusselier et al. (2019) Lee et al. (2018) Kim et al. (2010a)[a] Paramanathan et al. (2013)[a] Choi et al. (2015)[a] Moro-Sibilot et al. (2015) Kubota et al. (2009) Milella et al. (2012) Chang et al. (2010)[a] Kubota et al. (2009)
	Non-large-cell carcinoma was associated with better OS	Younes et al. (2011)[a]
	Survival after second-line therapy was negatively influenced by histology other than ADC	Zietemann and Duell (2011)
	Histology other than ADC influenced PFS after second-line therapy	Zietemann and Duell (2011)
	Lower OS was significantly associated with non-ADC and non-squamous histology	Dumenil et al. (2018)[a]
	Other (not squamous cell carcinoma or ADC) histology was associated with decreased OS	Kim et al. (2010b)[a]
	Poor histologic grade was associated with decreased OS	Kim et al. (2010b)[a]
	ADC/bronchioloalveolar carcinoma/mixed histology was associated with better response and longer TTP	Ludovini et al. (2011)
	Histology predicted response	Sim et al. (2018) (Fukuoka 2003 IDEAL I)
	Pathological type was correlated to PFS	Zheng et al. (2014)[a]

	Histopathology was considered a prognostic factor for survival and OS after second-line treatment	Sau et al. (2013)[a]
Tumour shrinkage	Early tumour shrinkage was defined as a > 10% reduction by the first evaluation and was associated with significantly longer median PFS and OS	Kawachi et al. (2019)
	Patients with tumour regression (SD-/0) had longer PFS and OS than patients with tumour enlargement (SD+)	Zhang et al. (2012)[a]
Tumour classification	Higher TNM classification of malignant tumour staging-T factor was associated with significantly shorter PFS	Naoki et al. (2017)
Measurable disease	Disease control was an independent prognostic factor of survival for the SD subgroup of patients	Zhang et al. (2012) Shukuya et al. (2016)
	Survival outcomes after subsequent line of therapy was negatively influenced by no DC after previous line of therapy	Zietemann and Duell (2011)
	Median PFS in patients with DC after second-line treatment was longer than those without DC	Zietemann and Duell (2011)
	Tumour response (DC) was associated with better OS	Lie et al. (2011)
	Response (SD + PR vs PD) was related with both OS and PFS	Duan et al. (2017)
	OS of DC group was significantly higher than progression (PD) groups	Kim et al. (2010a)
	Good response (PR and SD) to a first-line CT was identified as a favourable factor of PFS	Kim et al. (2010a)
	There was a significant difference in survival from the date of CT at 5 to 9 weeks between patients with PR/stable disease and patients who had PD or were NE	Shukuya et al. (2016)
	Progression-free status at 8, 16, and 24 weeks significantly predicted OS	Shukuya et al. (2016)
Toxicity	Toxicity grade 1-3 was associated with longer disease-free survival and longer OS	Martin et al. (2017)

	Presence of skin toxicity (grade 3>grade2>grade1>no toxicity) had a significant influence on OS, with presence of skin rash leading to an increase in median OS with gefitinib	Acharyya et al. (2012)
	Absence of skin rash was associated with decreased OS with Tarceva	Kim et al. (2010b)
	Absence of skin rash was associated with decreased PFS with Tarceva	Kim et al. (2010b)
	Significantly higher rates of severe nausea/vomiting and diarrhoea were recorded in the first-line for cohort B compared to cohort A	Agelaki et al. (2010)
Tumour size	Tumour size regression was an independent prognostic factor of survival for patients with stable disease	Zhang et al. (2012)
	The presence of advanced tumour staging (T4 vs T3 + T2) was significantly associated with poor OS	Bacha et al. (2017)[a]
Race	Objective tumour response rate was higher for Japanese patients versus non-Japanese patients (Fukuoka 2003 IDEAL I)	Sim et al. (2018)

Abbreviations: ADC: adenocarcinoma; AE: adverse event; ALK: anaplastic lymphoma receptor tyrosine kinase gene; ALKi: anaplastic lymphoma receptor tyrosine kinase gene inhibitor; BMI: body mass index; BOR: best overall response; CNS: central nervous system; CR: complete response; CRT: chemoradiotherapy; CS: corticosteroids; CT: chemotherapy; DC: disease control; DCR: disease control rate; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; ESMO: European Society for Medical Oncology; HER-2: human epidermal growth factor receptor 2; ICI: immune checkpoint inhibitor; KRAS: Kirsten rat sarcoma; M1a: pulmonary contralateral metastases or pleural/pericardial effusion; MTC: medullary thyroid cancer; NSCLC: non-small cell lung cancer; ORR: overall response rate; OS: overall survival; pAKT: phosphorylated-Serine473-AKT; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PD: progressive disease; PD-L1: programmed death-ligand 1; PFS: progression-free survival; PR: partial response; PS: performance status; PST: palliative systemic therapy; *RAS*: rat sarcoma; *RET*: rearranged during transfection proto-oncogene gene; ROS1: ROS proto-oncogene 1, receptor tyrosine kinase; RR: response rate; SCS: simplified comorbidity score; SD: stable disease; T1/T2/T3/T4: size and/or extension of the primary tumour; TKI: tyrosine kinase inhibitor; TNM: Tumour, Node, Metastasis Classification of Malignant Tumors; TTP: time to progression.

Appendix D: First-line studies

D.1 List of included first-line studies

Table 42. List of included first-line studies

S.No.	Trial Name/NCT Number/ Trial Registration Number/ Author (Year)	RefID	Primary reference	RefID	Secondary reference
1	Gronberg (2009)	*	Grønberg BH, Bremnes RM, Fløtten O, Amundsen T, Brunsvig PF, Hjelde HH, Kaasa S, von Plessen C, Stornes F, Tollåli T, Wammer F. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. Journal of clinical oncology. 2009 Jul 1;27(19):3217-24.		
2	Kader (2013)	*	Kader YA, Le Chevalier T, El-Nahas T, Sakr A. Comparative study analysing survival and safety of bevacizumab/carboplatin/paclitaxel and cisplatin/pemetrexed in chemotherapy-naive patients with advanced non-squamous bronchogenic carcinoma not harboring EGFR mutation. OncoTargets and therapy. 2013;6:803.		
3	Rodrigues-Periera (2011)	*	Rodrigues-Pereira J, Kim JH, Magallanes M, Lee DH, Wang J, Ganju V, Martínez-Barrera L, Barraclough H, Van Kooten M, Orlando M. A randomised phase 3 trial comparing pemetrexed/carboplatin and docetaxel/carboplatin		

S.No.	Trial Name/NCT Number/ Trial Registration Number/ Author (Year)	RefID	Primary reference	RefID	Secondary reference
			as first-line treatment for advanced, nonsquamous non-small cell lung cancer. Journal of Thoracic Oncology. 2011 Nov 1;6(11):1907-14.		
4	Scagliotti (2008)	*	Scagliotti GV, Parikh P, Von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. Journal of clinical oncology. 2008 Jul 20;26(21):3543-51.	*	Novello S, Pimentel FL, Douillard JY, O'Brien M, von Pawel J, Eckardt J, Liepa AM, Simms L, Visseren-Grul C, Paz-Ares L. Safety and resource utilization by non-small cell lung cancer histology: results from the randomised phase III study of pemetrexed plus cisplatin versus gemcitabine plus cisplatin in chemonaive patients with advanced non-small cell lung cancer. Journal of Thoracic Oncology. 2010 Oct 1;5(10):1602-8.
5	Schuette (2013)	*	Schuette WH, Gröschel A, Sebastian M, Andreas S, Müller T, Schneller F, Guetz S, Eschbach C, Bohnet S, Leschinger MI, Reck M. A randomised phase II study of pemetrexed in combination with cisplatin or carboplatin as first-line therapy for patients with locally advanced or metastatic non–small-cell lung cancer. Clinical lung cancer. 2013 May 1;14(3):215-23.		
6	Treat (2010)	*	Treat JA, Gonin R, Socinski MA, Edelman MJ, Catalano RB, Marinucci DM, Ansari R, Gillenwater HH, Rowland KM, Comis RL, Obasaju CK. A randomised, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell	*	Treat J, Edelman MJ, Belani CP, Socinski MA, Monberg MJ, Chen R, Obasaju CK. A retrospective analysis of outcomes across histological subgroups in a three-arm phase III trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin for advanced non-small cell lung cancer. Lung cancer. 2010 Dec 1;70(3):340-6.

S.No.	Trial Name/NCT Number/ Trial Registration Number/ Author (Year)	RefID	Primary reference	RefID	Secondary reference
			lung cancer. Annals of oncology. 2010 Mar 1;21(3):540-7.		
7	Zhang (2013)	*	Zhang X, Lu J, Xu J, Li H, Wang J, Qin Y, Ma P, Wei L, He J. Pemetrexed plus platinum or gemcitabine plus platinum for advanced non‐small cell lung cancer: final survival analysis from a multicenter randomised phase II trial in the East Asia region and a meta‐analysis. Respirology. 2013 Jan;18(1):131-9.		
8	SICOG	*	Comella P, Chiuri VE, De Cataldis G, Filippelli G, Maiorino L, Vessia G, Cioffi R, Mancarella S, Putzu C, Greco E, Palmeri L. Gemcitabine combined with either pemetrexed or paclitaxel in the treatment of advanced non-small cell lung cancer: a randomised phase II SICOG trial. Lung Cancer. 2010 Apr 1;68(1):94-8.		
9	Yu (2014)	*	Yu H, Zhang J, Wu X, Luo Z, Wang H, Sun S, Peng W, Qiao J, Feng Y, Wang J, Chang J. A phase II randomised trial evaluating gefitinib intercalated with pemetrexed/platinum chemotherapy or pemetrexed/platinum chemotherapy alone in unselected patients with advanced non-squamous non-small cell lung cancer. Cancer biology & therapy. 2014 Jul 1;15(7):832-9.		
10	ET	#	Lee SM, Falzon M, Blackhall F, Spicer J, Nicolson M, Chaudhuri A, Middleton G, Ahmed S, Hicks J, Crosse B, Napier M. Randomised prospective		

S.No.	Trial Name/NCT Number/ Trial Registration Number/ Author (Year)	RefID	Primary reference	RefID	Secondary reference
			biomarker trial of ERCC1 for comparing platinum and nonplatinum therapy in advanced non-small-cell lung cancer: ERCC1 trial (ET). Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2017 Feb;35(4):402-11.		
11	TRAIL	#	Park CK, Oh IJ, Kim KS, Choi YD, Jang TW, Kim YS, Lee KH, Shin KC, Jung CY, Yang SH, Ryu JS. Randomised phase III study of docetaxel plus cisplatin versus pemetrexed plus cisplatin as first-line treatment of nonsquamous non–small-cell lung cancer: a TRAIL trial. Clinical lung cancer. 2017 Jul 1;18(4):e289-96.		
12	Kim (ESMO 2014)	*	Kim Y, Oh I, Kim K, Jang T, Choi YD, Kim YS, Lee K, Shin K, Jung CY, Yang S, Jang S. A randomised phase iii study of docetaxel plus cisplatin versus pemetrexed plus cisplatin in first line non-squamous non-small cell lung cancer (NSQ-NSCLC). Annals of Oncology. 2014 Sep 1;25:v1.		

Footnotes: *Original SLR (SLR1). #First update (SLR2) @Second update (SLR3) $ Third update (SLR4).
Abbreviations: SLR: systematic literature review.

D.2 Treatment characteristics

Table 43. Characteristics of first-line treatments

Study ID	Intervention	Intervention	Dose	Regimen	Median no of cycles	Intervention	Dose	Regimen	Median no of cycles	Intervention	Dose	Regimen	Median no of cycles
Kim 2014	PEM+CIS	PEM	500 mg/ m^2	Q3W	Mean cycle: 3.4, range: 1-6	CIS	70 mg/ m^2	Q3W	Mean cycle: 3.4, range: 1–6	-	-	-	-
	DOC+CIS	DOC	60 mg/ m^2	Q3W	Mean cycle: 3.2, range: 1-6	CIS	70 mg/ m^2	Q3W	Mean cycle: 3.2, range: 1–6	-	-	-	-
TRAIL	PEM+CIS	PEM	500 mg/ m^2	Q3W	Max of 4 cycles	CIS	70 mg/m2	Q3W	Max of 4 cycles	-	-	-	-
	DOC+CIS	DOC	60mg/ m^2	Q3W	Max of 4 cycles	CIS	70 mg/m2	Q3W	Max of 4 cycles	-	-	-	-
Yu 2014	GEF+PEM+(CIS or CARB)	GEF	250 mg	QD	Max of 6 cycles	PEM	500 mg/ m^2	Q3W	Treatment continued until disease progression, unacceptable toxicity, or completion of a maximu	CIS or CARB	75 mg/ m^2 or AUC 5	Both Q3W	Treatment continued until disease progression, unacceptable toxicity, or completion of a maximu

Study ID	Intervention	Intervention	Dose	Regimen	Median no of cycles	Intervention	Dose	Regimen	Median no of cycles	Intervention	Dose	Regimen	Median no of cycles
									m of 6 cycles				m of 6 cycles
	PEM+(CIS or CARB)	PEM	500 mg/ m^2	Q3W	Max of 6 cycles	CIS or CARB	75 mg/ m^2 or AUC 5	Both Q3W	Treatment continued until disease progression, unacceptable toxicity, or completion of a maximum of 6 cycles	-	-	-	-
Zhang 2013	PEM+CIS	PEM	500 mg/ m^2	Q3W	5	CIS	75 mg/ m^2	Q3W.	5	-	-	-	-
	GEM+CIS	CIS	75 mg/ m^2	Q3W	4	GEM	1000 mg /m^2	Q3W	4	-	-	-	-
ET	PEM+CIS	PEM	500mg/ m^2	Q3W.	Max of 6 cycles	CIS	75 mg/m2	Q3W	-	-	-	-	-
	PAC+PEM	PAC	175 mg/ m^2	Q3W.	Max of 6 cycles	PEM	500 mg/m2	Q3W	-	-	-	-	-
Gronberg 2009	PEM+CARB	PEM	500mg/ m^2	Q3W	-	CARB	AUC 5	Q3W	-	-	-	-	-
	GEM+CARB	GEM	1000mg/ m^2	Q3W	-	CARB	AUC 5	Q3W	-	-	-	-	-

Study ID	Intervention	Intervention	Dose	Regimen	Median no of cycles	Intervention	Dose	Regimen	Median no of cycles	Intervention	Dose	Regimen	Median no of cycles
Kader 2013	BEV+CARB +PAC	BEV	7.5 mg/kg	Q4W	-	CARB	AUC 5	Q4W	-	PAC	60 mg/m^2	Q4W	-
	CIS+PEM	CIS	75 mg/m^2	Q3W	-	PEM	500 mg/ m^2	Q3W	-	-	-	-	-
Rodrigues-Pereira 2011	PEM+CARB	PEM	500 mg/ m^2	Q3W	Max of 6 cycles	CARB	AUC 5	Q3W	Max of 6 cycles	-	-	-	Max of 6 cycles or until progressive disease, unacceptable toxicity
	DOC+CARB	DOC	75 mg/m^2	Q3W	Max of 6 cycles	CARB	AUC 5	Q3W	Max of 6 cycles	-	-	-	-
Scagliotti 2008	PEM+CIS	PEM	500 mg/m^2	Q3W	5	CIS	75 mg/m^2	Q3W	5	-	-	-	-
	GEM+CIS	GEM	1250mg/ m^2	Q3W	5	CIS	75 mg/m^2	Q3W	5	-	-	-	-
Schuette 2013	PEM+CIS	PEM	500 mg/ m^2	Q3W	4	CIS	75 mg/m^2	Q3W	4	-	-	-	-
	PEM+CARB	PEM	500 mg/ m^2	Q3W	6	CARB	AUC 6	Q3W	6	-	-	-	-
SICOG	PAC+GEM	PAC	120 mg/ m^2	Q3W	5	GEM	1000 mg /m^2	Q3W	5	-	-	-	-
	GEM+PEM	GEM	1250 mg/ m^2	Q3W	4	PEM	500 mg/ m^2	Q3W	4	-	-	-	-
Treat 2010	GEM+CARB	GEM	1000 mg/ m^2	Q3W	4	CARB	AUC 5.5	Q3W	4	-	-	-	-

Study ID	Intervention	Intervention	Dose	Regimen	Median no of cycles	Intervention	Dose	Regimen	Median no of cycles	Intervention	Dose	Regimen	Median no of cycles
	GEM+PAC	GEM	1000 mg/ m^2	Q3W	4	PAC	200 mg/ m^2	Q3W	4	-	-	-	-
	PAC+CARB	PAC	225 mg/ m^2	Q3W	4	CARB	AUC 6	Q3W	4	-	-	-	-

D.3 Study characteristics

Table 44. Study characteristics (first-line studies)

Study ID	Primary publication	Associated publication	Clinical trial number	Study location	Study phase	Study blinding	Eligible AJCC stage	Eligible ECOG/ WHO PS	Excluded histology	Excluded biomarker status
Kim 2014	Kim ESMO 2014^*	-	NCT01282151	Korea	III	Open-label	IIIB or IV	0 to 2	Squamous	-
TRAIL	Park 2017#	-	NCT01282151	Korea	III	Open-label	IIIB or IV	0 to 2	Squamous	EGFR
Yu 2014	Yu 2014*	-	NCT01769066	China	II	Open-label	IIIB or IV	0 or 1	Squamous	-
Zhang 2013	Zhang 2013*	-	-	China	II	-	IIIB, IV or recurrent	0 or 1	-	-
ET	Lee 2017#	-	-	United Kingdom	III	-	IIIB or IV	0 or 1	-	-
Gronberg 2009	Gronberg 2009*	-	-	Norway	III	Open-label	IIIB (ineligible for curative radiotherapy) or IV	0 to 2	-	-
Kader 2013	Kader 2013*	-	-	Egypt	II	-	IIIB or IV	0 to 2	Squamous	EGFR
Rodrigues-Pereira 2011	Rodrigues-Pereira 2011*	-	NCT00520676	Australia, Brazil, China, Mexico,	III	Open-label	IIIB or IV	0 to 2	Squamous	-

Study ID	Primary publication	Associated publication	Clinical trial number	Study location	Study phase	Study blinding	Eligible AJCC stage	Eligible ECOG/ WHO PS	Excluded histology	Excluded biomarker status
				South Korea, and Taiwan						
Scagliotti 2008	Scagliotti 2008*	Novello 2010 *	-	-	III	-	IIIB (not amenable to curative treatment) or IV	0 or 1	-	-
Schuette 2013	Schuette 2013*	-	NCT00402051	Germany	II	Open-label	IIIB or IV	0 or 1	-	-
SICOG	Comella 2010*	-	-	Italy	II	-	IIIB or IV	0 to 1	-	-
Treat 2010	Treat 2010a*	Treat 2010b*	NCT00054392	United States	III	-	IIIB, IV or recurrent	0 or 1	-	-

D.4 Baseline characteristics

Table 45. Baseline characteristics - first-line studies (age, sex, race, ethnicity and smoking status)

Trial Name, Primary Author Year	Intervention	N randomised/ ITT	Baseline population	Age (years)					Female		White		Black		Asian		Other race		Hispanic		Smoking status (%)	
				Mean	SD	Median	Min	Max	n	%	n	%	n	%	n	%	n	%	n	%	Never	Current or previous
Kim 2014	PEM+CIS	77/ -	77	63	8.9	-	-	-	-	-	-	-	-	-	77 †	100	-	-	-	-	-	-

Trial Name, Primary Author Year	Intervention	N randomised/ ITT	Baseline population	Age (years)					Female		White		Black		Asian		Other race		Hispanic		Smoking status (%)	
				Mean	SD	Median	Min	Max	n	%	n	%	n	%	n	%	n	%	n	%	Never	Current or previous
	DOC+CIS	72/ -	72	63.8	9.8	-	-	-	-	-	-	-	-	-	72†	100	-	-	-	-	-	-
TRAIL, Park 2017	PEM+CIS	80/77	77	63	8.9	-	-	-	24	31.2	-	-	-	-	-	-	-	-	-	-	27.5	72.5
	DOC+CIS	76/71	71	63.6	9.7	-	-	-	21	29.6	-	-	-	-	-	-	-	-	-	-	28.6	71.4
Yu 2014	GEF+PEM+(CIS or CARB)	58/ -	58	55.3	-	-	36	72	25	43	-	-	-	-	58†	100	-	-	-	-	50	50
	PEM+(CIS or CARB)	59/ -	59	54.9	-	-	33	70	34	58	-	-	-	-	59†	100	-	-	-	-	66	34
Zhang 2013‡	PEM+CIS	128/127	127	-	-	54	33	73	49	38.58	-	-	-	-	127†	100	-	-	-	-	-	-
	GEM+CIS	126/124	124	-	-	55	26	71	47	37.9	-	-	-	-	124†	100	-	-	-	-	-	-
ET, Lee 2017	PEM+CIS	235/230	230	-	-	63	39	79	97	42	-	-	-	-	-	-	-	-	-	-	9	91

Trial Name, Primary Author Year	Intervention	N randomised/ ITT	Baseline population	Age (years)					Female		White		Black		Asian		Other race		Hispanic		Smoking status (%)	
				Mean	SD	Median	Min	Max	n	%	n	%	n	%	n	%	n	%	n	%	Never	Current or previous
	PAC+PEM	236/234	234	-	-	64	35	79	103	44	-	-	-	-	-	-	-	-	-	-	10	90
Gronberg 2009‡	PEM+CARB	225/219	219	-	-	64	35	90	96	44	-	-	-	-	-	-	-	-	-	-	10	90*
	GEM+CARB	221/217	217	-	-	66	25	84	89	41	-	-	-	-	-	-	-	-	-	-	5	95*
Kader 2013	BEV+CARB +PAC	20/ -	20	53.35	-	-	39	69	5	25	-	-	-	-	-	-	-	-	-	-	15	85
	CIS+PEM	21/ -	21	51.62	-	-	31	67	6	28.6	-	-	-	-	-	-	-	-	-	-	9.5	90.5
Rodrigues-Pereira 2011	PEM+CARB	128/118	118	-	-	60.1	27.9	83.1	42	39.6	39	36.8	5	4.7	45	42.5	-	-	17	16	32.1	67.9*
	DOC+CARB	132/127	127	-	-	58.9	31.4	78.4	55	52.4	35	33.3	4	3.8	44	41.9	-	-	22	21	39	61*
Scagliotti 2008	PEM+CIS	618/618	618	-	-	60.7	-	-	-	36	-	76	-	-	-	14	-	10	-	-	18	70

Trial Name, Primary Author Year	Intervention	N randomised/ ITT	Baseline population	Age (years)					Female		White		Black		Asian		Other race		Hispanic		Smoking status (%)	
				Mean	SD	Median	Min	Max	n	%	n	%	n	%	n	%	n	%	n	%	Never	Current or previous
	GEM+CIS	634/634	634	-	-	59.9	-	-	-	33	-	79	-	-	-	12	-	10	-	-	17	71
Schuette 2013‡	PEM+CIS	66/ -	n=65*	-	-	64	42	78	23	35.4	65	100	0	0	0	0	0	0	-	-	13.8	86.2
	PEM+CARB	67/ -	n=65*	-	-	63	45	80	19	29.2	65	100	0	0	0	0	0	0	-	-	10.8	89.2
SICOG, Comella 2010‡	PAC+GEM	55/54	54	-	-	64	44	77	8	15	-	-	-	-	-	-	-	-	-	-	-	-
	GEM+PEM	53/51	51	-	-	66	40	79	11	22	-	-	-	-	-	-	-	-	-	-	-	-
Treat 2010‡	GEM+CARB	379/379	379	-	-	64.1	37	89	158	41.7	326	86	47	12.4	-	-	6	1.6	-	-	-	-
	GEM+PAC	377/377	377	-	-	64.3	33	91	141	37.4	329	87.3	42	11.1	-	-	6	1.6	-	-	-	-

Trial Name, Primary Author Year	Intervention	N randomised/ ITT	Baseline population	Age (years)					Female		White		Black		Asian		Other race		Hispanic		Smoking status (%)	
				Mean	SD	Median	Min	Max	n	%	n	%	n	%	n	%	n	%	n	%	Never	Current or previous
	PAC+CARB	379/379	379	-	-	64.1	39	85	148	39.1	317	83.6	49	12.9	-	-	12	3.2	-	-	-	-

Table 46. Baseline characteristics II - first-line studies (histology, ECOG/WHO PS, AJCC stage and biomarker status)

Trial Name, Primary Author Year	Intervention	Baseline population	Histology								ECOG/ WHO PS						AJCC stage				EGFR+	
			nsq NSCLC		nsq NSCLC subtypes						0		1		2		IIIB		IV			
					Adeno-carcinoma		Large cell		Adenosquamous carcinoma													
			n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%	n	%	n	%
Kim 2014	PEM+CIS	77	77	100	75	97.40*	0	0	-	-	14	18.18*	55	71.43*	8	10.39*	5	6.49*	72	93.51*	-	-
	DOC+CIS	72	72	100	69	95.83*	1	1.39*	-	-	17	23.61*	48	66.67*	7	9.72*	3	4.17*	69	95.83*	-	-

Trial Name, Primary Author Year	Intervention	Baseline population	Histology								ECOG/ WHO PS						AJCC stage				EGFR+	
			nsq NSCLC		nsq NSCLC subtypes						0		1		2		IIIB		IV			
					Adeno-carcinoma		Large cell		Adenosquamous carcinoma													
			n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%	n	%	n	%
TRAIL, Park 2017	PEM+CIS	77	77	100	77	100.00	0	0.00	-	-	14	18.2	55	71.4	8	10.4	5	6.5	72	93.5	-	-
	DOC+CIS	71	71	100	68	95.77	1	1.41	-	-	17	23.9	47	66.2	7	9.9	3	4.2	68	95.8	-	-
Yu 2014	GEF+PEM+(CIS or CARB)	58	58	100	58	100	0	0	-	-	8	14	50	86	0	0	5	9	53	91	16*	27.59*
	PEM+(CIS or CARB)	59	59	100	59	100	0	0	-	-	9	15	50	85	0	0	5	8	54	92	19*	32.2*
Zhang 2013‡	PEM+CIS	127	99*	77.95	94	74.02	5	3.94	-	-	43	33.86	84	66.14	0	0	45	35.43	82	64.57	-	-
	GEM+CIS	124	90*	72.58*	88	70.97	2	1.61	-	-	44	35.48	80	64.52	0	0	35	28.23	89	71.77	-	-
ET, Lee 2017	PEM+CIS	230	230	100	-	-	-	-	-	-	101	44	129	56	-	-	45	20	185	80	-	-
	PAC+PEM	234	234	100	-	-	-	-	-	-	107	46	127	54	-	-	49	21	185	79	-	-

Trial Name, Primary Author Year	Intervention	Baseline population	Histology								ECOG/ WHO PS						AJCC stage				EGFR+	
			nsq NSCLC		nsq NSCLC subtypes						0		1		2		IIIB		IV			
					Adeno-carcinoma		Large cell		Adenosquamous carcinoma													
			n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%	n	%	n	%
Gronberg 2009‡	PEM+CARB	219	-	-	109	50	18	8.00	-	-	-	-	-	-	47	22	63	29	156	71	-	-
	GEM+CARB	217	-	-	108	50	13	6.00	-	-	-	-	-	-	49	23	61	28	156	72	-	-
Kader 2013	BEV+CARB+PAC	20	20	100	15	75	-	-	4	20	-	-	-	-	4	20	5	25	15	75	0	0
	CIS+PEM	21	21	100	16	76.2	-	-	3	14.3	-	-	-	-	7	33.3	4	19	17	81	0	0
Rodrigues-Pereira 2011	PEM+CARB	118	106	100	90	84.9	10	9.4	-	-	31	29.2	60	56.6	15	14.2	17	16	89	84	-	-
	DOC+CARB	127	105	100	91	86.7	9	8.6	-	-	28	26.7	60	57.1	17	16.2	23	21.9	82	78.1	-	-
Scagliotti 2008	PEM+CIS	618	618	100	436	70.55*	76	12.30*	-	-	-	35	-	65	-	-	-	21	-	79	-	-
	GEM+CIS	634	634	100	411	64.83*	77	12.15*	-	-	-	37	-	62	-	-	-	23	-	77	-	-
Schuette 2013‡	PEM+CIS	65 (randomised	53	81.5	-	-	-	-	-	-	40	61.5	25	38.5	0	0	5	7.6	61	92.4	-	-

Trial Name, Primary Author Year	Intervention	Baseline population	Histology								ECOG/ WHO PS						AJCC stage				EGFR+	
			nsq NSCLC		nsq NSCLC subtypes						0		1		2		IIIB		IV			
					Adeno-carcinoma		Large cell		Adenosquamous carcinoma													
			n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%	n	%	n	%
		and treated)																				
	PEM+CARB	65 (randomised and treated)	52	80	-	-	-	-	-	-	45	69.2	20	30.8	0	0	9	13.4	58	86.6	-	-
SICOG, Comella 2010‡	PAC+GEM	54	25*	46.30*	24*	44	1	2	-	-	15	28	39	72	0	0	24*	44.44*	30	56	-	-
	GEM+PEM	51	21*	41.18*	19*	37	2	4	-	-	12	24	39	76	0	0	19*	37.25*	32	63	-	-
Treat 2010‡	GEM+CARB	379	312	82.3	192	50.66*	15	3.96*	-	-	124	32.7	253	66.8	1	0.3	38	10	341	90	-	-
	GEM+PAC	377	303	80.4	167	44.30*	18	4.77*	-	-	159	42.2	215	57	2	0.5	38	10.1	339	88.9	-	-
	PAC+CARB	379	318	83.9	196	51.72*	12	3.17*	-	-	144	38	231	60.9	1	0.3	40	10.6	339	89.4	-	-

D.5 Efficacy: Response rates

Table 47. Median follow-up and response rates (first-line studies)

Study ID	Intervention	Median follow-up (months)	Response														
			ORR			CR			PR			SD			PD		
			N	N	%	N	n	%	N	n	%	N	n	%	N	n	%
Kim 2014	PEM+CIS	-	-	-	-	-	-	-	77	24	31.2	77	33	42.9*	77	10	13*
	DOC+CIS	-	-	-	-	-	-	-	72	24	33.3	72	25	34.7*	72	15	20.8*
TRAIL, Park 2017	PEM+CIS	-	68	24	35.2	-	-	-	77	24	31.2	77	34	44.2	77	10	12.9
	DOC+CIS	-	64	24	37.5	-	-	-	71	24	33.8	71	25	35.2	71	15	21.1
Yu 2014	GEF+PEM+(CIS or CARB)	-	54	27	50	-	-	-	-	-	-	-	-	-	-	-	-
	PEM+(CIS or CARB)	-	57	27	47.4	-	-	-	-	-	-	-	-	-	-	-	-
ET, Lee 2017	PEM+CIS	30	230	-	30.4	230	2	0.9	230	68	29.6	230	84	36.5	230	16	7.0
	PAC+PEM	30	234	-	35.7	234	1	0.4	234	64	27.4	234	86	36.8	234	31	13.2
Gronberg 2009†	PEM+CARB	18.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	GEM+CARB	18.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kader 2013	BEV+CARB+PAC	-	-	-	-	-	-	-	20	12	60*	20	6	30*	-	-	-
	CIS+PEM	-	-	-	-	-	-	-	21	10	47.62*	21	9	42.86*	-	-	-

Study ID	Intervention	Median follow-up (months)	Response														
			ORR			CR			PR			SD			PD		
			N	N	%	N	n	%	N	n	%	N	n	%	N	n	%
Rodrigues-Pereira 2011	PEM+CARB	23.9	106	-	34	106	1	0.94 *	-	-	-	-	-	-	-	-	-
	DOC+CARB	20.9	105	-	22.9	105	0	0	-	-	-	-	-	-	-	-	-
SICOG, Comella 2010	PAC+GEM	22	24 ‡	-	38	-	-	-	-	-	-	-	-	-	-	-	-
	GEM+PEM	22	19 ‡	-	26	-	-	-	-	-	-	-	-	-	-	-	-
Treat 2010	GEM+CARB	8.2	312	-	25.32	-	-	-	-	-	-	-	-	-	-	-	-
	GEM+PAC	8.2	303	-	31.35	-	-	-	-	-	-	-	-	-	-	-	-
	PAC+CARB	8.2	318	-	26.73	-	-	-	-	-	-	-	-	-	-	-	-
Yu 2014	GEF+PEM+(CIS or CARB)	-	54	27	50	-	-	-	-	-	-	-	-	-	-	-	-
	PEM+(CIS or CARB)	-	57	27	47.4	-	-	-	-	-	-	-	-	-	-	-	-

D.6 Efficacy: Overall survivals

Table 48. Overall survival (first-line studies)

Study ID	Intervention	Overall Survival										
		Median (months)	L95% CI	U95% CI	Comparator/ reference	HR	L95% CI	U95 %CI	p value	1 year %	2 year %	KM availability
ET, Lee 2017	PEM+CIS	10.5	-	-	Reference	-	-	-	-	-	-	Yes

	PAC+PEM	8.8	-	-	Comparator	1.06	0.87	1.29	0.57	-	-	Yes
Gronberg 2009†	PEM+CARB	7.8	5.4	10.1	Reference	-	-	-	-	-	-	Yes
	GEM+CARB	7.5	6.0	9.4	Comparator	-	-	-	0.77	-	-	Yes
Kader 2013	BEV+CARB+PAC	16.01	11.47	20.55	Comparator	-	-	-	-	80	20	Yes
	CIS+PEM	16.07	14.66	17.49	Reference	-	-	-	0.89	85.7	33	Yes
Kim ESMO 2014	PEM+CIS	19.7	10.8	28.6	-	-	-	-	-	-	-	No
	DOC+CIS	28	7.5	48.5	-	-	-	-	-	-	-	No
Rodrigues-Pereira 2011	PEM+CARB	14.9	12.2	19	Comparator	0.93	0.66	1.32	0.698	-	-	Yes
	DOC+CARB	14.7	10.8	19.8	Reference	-	-	-	-	-	-	Yes
Scagliotti 2008†	PEM+CIS	11.8	10.4	13.2	Comparator	0.81	0.70	0.94	0.005	-	-	Yes
	GEM+CIS	10.4	9.6	11.2	Reference	-	-	-	-	-	-	Yes
Schuette 2013	PEM+CIS	11.9	9.4	15.2	-	-	-	-	-	-	-	Yes
	PEM+CARB	8.5	6	13.3	-	-	-	-	-	-	-	Yes
TRAIL, Park 2017	PEM+CIS	11.7	8.6	14.8	-	-	-	-	-	-	-	Yes
	DOC+CIS	13.3	8.1	18.5	-	-	-	-	-	-	-	Yes
Treat 2010	GEM+CARB	8.2	7.3	9.5	Comparator	0.96	0.81	1.13	0.61	-	-	Yes
	GEM+PAC	8.4	7.2	9.8	Comparator	0.97	0.82	1.14	0.7	-	-	Yes
	PAC+CARB	8.3	7.3	9.8	Reference	-	-	-	-	-	-	Yes
Yu 2014	GEF+PEM+(CIS or CARB)	25.4	-	-	Comparator	0.84	0.47	1.48	0.54	-	-	Yes
	PEM+(CIS or CARB)	20.8	-	-	Reference	-	-	-	-	-	-	Yes
Zhang 2013	PEM+CIS	16.69	12.98	20.43	Comparator	0.95	0.68	1.35	0.993	-	-	No

	GEM+CIS	16.66	13.57	20.49	Reference	-	-	-	-	-	-	No

D.7 Efficacy: Progression-free survival

Table 49. Progression-free survival (first-line studies)

Study ID	Intervention	Progression-free survival								
		Median (months)	L95% CI	U95% CI	Comparator/ reference	HR	L95% CI	U95% CI	p value	KM availability
ET, Lee 2017	PEM+CIS	6.9	-	-	Reference	-	-	-	-	Yes
	PAC+PEM	5.5	-	-	Comparator	1.16	0.96	1.4	0.13	Yes
Kader 2013	BEV+CARB+PAC	6	5	7	Comparator	-	-	-	-	Yes
	CIS+PEM	6	4	8	Reference	-	-	-	0.978	Yes
Kim ESMO 2014	PEM+CIS	4.7	4.4	5.1	-	-	-	-	-	No
	DOC+CIS	4.6	3.7	5.6	-	-	-	-	-	No
Rodrigues-Pereira 2011	PEM+CARB	5.8	4.8	6.4	Comparator	0.91	0.67	1.23	0.534	Yes
	DOC+CARB	6	4.8	6.6	Reference	-	-	-	-	Yes
Scagliotti 2008†	PEM+CIS	5.3	4.8	5.7	Comparator	0.90	0.79	1.02	-	Yes
	GEM+CIS	4.7	4.4	5.4	Reference	-	-	-	-	Yes
Schuette 2013	PEM+CIS	6.4	4.7	7.5	-	-	-	-	-	Yes
	PEM+CARB	4.7	2.9	5.9	-	-	-	-	-	Yes
TRAIL, Park 2017	PEM+CIS	4.7	4.4	5	-	-	-	-	-	Yes
	DOC+CIS	4.4	3.7	5.1	-	-	-	-	-	Yes
Treat 2010*	GEM+CARB	4.4	3.8	5.3	Comparator	0.92	0.78	1.08	0.312	No
	GEM+PAC	4.4	3.7	5.4	Comparator	0.95	0.8	1.12	0.539	No

Study ID	Intervention	Progression-free survival								
		Median (months)	L95% CI	U95% CI	Comparator/ reference	HR	L95% CI	U95% CI	p value	KM availability
	PAC+CARB	4.4	3.9	5.1	Reference	-	-	-	-	No
Yu 2014	GEF+PEM+(CIS or CARB)	7.9	-	-	Comparator	0.88	0.56	1.37	0.57	Yes
	PEM+(CIS or CARB)	7	-	-	Reference	-	-	-	-	Yes

Appendix E: Model stress checklist

Table 50: Stress test checklist used for cost-effectiveness model validation

#	Test	Expected effect	Checked?	Observed effect	Action required?
1	Set initial number of patients to 0.	Costs and QALYs across all treatments should be 0.	Yes	As expected	No
2	Set initial number of patients to 1.	ICER should not change.	Yes	As expected	No
3	Set both treatment and comparator to same intervention.	Costs and QALYs across all treatments should be equal.	Yes	As expected	No
4	Set treatment to comparator(s), and comparator(s) to treatment	Costs and QALYs should be the same as the base case, but inverted.	N/A	The model does not allow swapping intervention and comparators	No
5	Set all efficacy data equal across treatments, and set disutility associated with adverse events to 0.	QALYs across all treatments should be equal.	Yes	As expected	No
6	Set mortality rate to 0% at all ages (and any other mortality in the model)	There are no deaths in the model.	Yes	As expected	No
7	Set mortality rate to 100% at all ages	All patients are dead in the first cycle.	Yes	As expected	No
8	Increase mortality rate	Costs are reduced.	Yes	As expected	No
9	Set the health state utilities the same for all states (if applicable, set AE disutilities to 0)	Life years to QALY ratio should be the same across all treatments.	Yes	As expected	No
10	Set disutility of adverse events to 0	Overall QALYs should decrease. QALYs of adverse events = 0. QALYs of health states should not change. Costs should not change.	Yes	As expected	No
11	Set the utilities for all health states to 0 and adverse events to 0	All QALYS = 0. Costs should not change.	Yes	As expected	No

12	Set the utilities for all health states to 1 and adverse events to 0	No difference between LYs and QALYs for each treatment arm. Costs should not change.	Yes	As expected	No
13	Halve all utilities and disutilities	ICERs should double.	Yes	As expected	No
14	Set the cost and utility consequences for adverse events and discontinuation to 0, then undo these changes and set all adverse event rates to 0	Results in both cases are the same. Costs and QALYs associated with AEs are 0.	Yes	As expected	No
15	Set adverse event and discontinuation rates to 0, then undo these changes and set adverse and discontinuation rates to a high level	The first scenario should result in lower costs (AE costs = 0), higher life years and greater QALYs (AE disutilities = 0) than the second. Other disaggregated results should not change.	Yes	As expected	No
16	Set (per-cycle) treatment discontinuation to 0%, then set to 100%	The first scenario should result in no patients staying on treatment after the first cycle, the second scenario should result in all patients remaining on treatment for the entire time horizon.	Yes	As expected	No
17	Decrease the utilities for all health states simultaneously whilst keeping event-based utility decrements constant	QALYs of health states are reduced. LYs and costs should not change.	Yes	As expected	No
18	Set all health state utilities <0 (i.e. negative)	QALYs decrease over time.	Yes	As expected	No
19	Set equal the effectiveness, utility and safety-related model inputs for all treatment options	No difference between LYs and QALYs for each treatment arm, at any given time.	Yes	As expected	No
20	Set the costs of treatments to 0	All treatments costs = 0. LYs, QALYs and other	Yes	As expected	No

		disaggregated cost results (excepted for subsequent treatment costs) should not change. Subsequent treatment costs should be lower.			
21	Double the costs of treatments	Treatment costs doubled. LYs, QALYs and other disaggregated cost results (excepted for subsequent treatment costs) should not change. Subsequent treatment costs should be higher.	Yes	As expected	No
22	Set relative dose intensity of treatments to 0	Drug acquisition costs should be 0.	Yes	As expected	No
23	Increase body weight and/or body surface area (only relevant for weight/BSA dependent dosing)	Treatment costs (for weight/BSA dependent treatments) are increased. LYs, QALYs and other disaggregated cost results (except for subsequent treatment costs) should not change. Subsequent treatment costs should be higher.	Yes	As expected	No
24	Set all administration costs to 0	All administration costs = 0. LYs, QALYs and other disaggregated cost results (except for subsequent treatment costs) should not change. Subsequent treatment costs should be lower.	Yes	As expected	No
25	Double all administration costs	Administration costs doubled. LYs, QALYs and other disaggregated cost results (except for subsequent treatment costs) should not change. Subsequent	Yes	As expected	No

		treatment costs should be higher.			
26	Set all monitoring/follow-up costs to 0	Monitoring/follow-up costs = 0. Other disaggregated cost results, LYs, and QALYs should not change.	Yes	As expected	No
27	Double all monitoring/follow-up costs.	Monitoring/follow-up costs doubled. Other disaggregated cost results, LYs, and QALYs should not change.	Yes	As expected	No
28	Set all disease management costs to 0	Disease management costs = 0. Other disaggregated cost results, LYs and QALYs should not change.	Yes	As expected	No
29	Double all disease management costs.	Disease management costs doubled. Other disaggregated cost results, LYs and QALYs should not change.	Yes	As expected	No
30	Alter the time horizon	Total costs and QALYS increase/decrease in accordance with longer/shorter horizons.	Yes	As expected	No
31	Increase average patient age	LYs and QALYs decrease	Yes	As expected	No
32	Alter subgroups	Model-dependent	N/A	N/A	No
33	Alter transition probabilities	Model-dependent	N/A	N/A (PSM not Markov)	No
34	Increase the OR/RR/HR baseline probabilities.	The probabilities of events derived from OR/RR/HR baselines probabilities should increase.	Yes	As expected	No
35	Set discount rates to 0%	Undiscounted results = discounted results.	Yes	As expected	No
36	Set discount rates to 100%	Costs and QALYs reduce significantly.	Yes	As expected	No
37	Increase inflation rates	Any cost inputs relying on inflation should increase.	N/A	N/A	No

38	Run the DSA/OWSA and check all input parameters affect results when values are changed	Any input parameters should affect the incremental QALYS, costs or both (unless it has an exactly equal effect on all arms in the model). Investigate parameters that do not change the ICER (or incremental costs/QALYs) from baseline. Cost parameters should only impact incremental costs. Utility parameters should only impact incremental QALYs. Efficacy parameters likely impact costs and QALYs.	Yes	As expected	No
39	Open model base case, check results. Reset input base case, check results	Results should not change after resetting inputs.	Yes	As expected	No
40	Record base case results. Change any inputs from default values, then reset inputs	Inputs should be reset to default values and results should restore to original value.	Yes	As expected	No
41	Check plots of OS/PFS/ToT extrapolations and KM curves (only relevant for PSMs)	All extrapolation curves (of both intervention and comparators) should be presented in plots. Extrapolations should be smooth curves.	Yes	As expected	No
42	Check base case OS/PFS/ToT extrapolations against KM curves (only relevant for PSMs)	The base case extrapolations should align with KM curves. PFS or ToT should not exceed OS.	Yes	As expected	No
43	Change the curve choice selected for OS/PFS/ToT for each treatment (only relevant for PSMs)	The graph which shows the selected extrapolation should change when curve choice changes.	Yes	As expected	No
44	Change OS curve choice for each treatment (only relevant for PSMs)	LYs and QALYs should change, but only for the “PD”	Yes	As expected	No

		health state and Total. Only results for the respective treatment should change unless HRs are used to derive other treatments (in which case those results should also change).			
45	Change PFS curve choice for each treatment (only relevant for PSMs)	Total LYs should not change (but distribution between the PF and PD health state should change). Overall and disaggregated QALYs can change. Only results for the respective treatment should change unless HRs are used to derive other treatments (in which case those results should also change).	Yes	As expected	No
46	Change ToT curve choice for each treatment (only relevant for PSMs)	Total LYs should not change. Treatment costs should change if ToT is used to determine treatment costs. QALYs should only change if there is a treatment-related utility parameter (e.g. disutility or utility for being on treatment). If utility values are only linked to progression (e.g. PF and PD health states), changing ToT curve choice should have no impact on QALYs. Only results for the respective treatment should change unless HRs are used to derive other treatments (in which case those results	N/A	N/A, Model does not include ToT curve	No

		should also change).			
47	Compare survival curves and the respective results of the treatments	Treatments with higher OS curves on the OS graph should have more LYs and likely more QALYs, and vice versa.	Yes	As expected	No
48	Set mortality and incidence rates to 0 (only relevant for BIMs)	Prevalence should be constant with time.	N/A	N/A, PSM	No
49	Set (patient) population inputs to 0 (only relevant for BIMs)	All BIM results should be 0.	N/A	N/A, PSM	No
50	Set all market shares of the intervention in the scenario with the intervention (only relevant for BIMs)	Budget Impact should be 0.	N/A	N/A, PSM	No

Abbreviations: AE: adverse events; BIM: budget impact model; BSA: body surface area; DSA: deterministic survival analysis; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; LY: life years; OS: overall survival; PFS: progression-free survival; PD: progressed disease; PSM: propensity score matching; QALY: quality-adjusted life years; RR: relative risk.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Selpercatinib for Lung cancer (non-small-cell, advanced, RET fusion, untreated) [ID4056]

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 and work in lung cancer patient care (information, support and advocacy activity). Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	As a result of the COVID pandemic, our contact with patients and carers has largely become virtual. The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	According to the National Lung Cancer Audit, the one year survival for lung cancer is 37%. Thus, this group of lung cancer patients have a particularly poor outlook. with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe. RET alterations are found in about 1% to 2% of patients with NSCLC. These patients tend to be younger and more likely to be light/non-smokers, as compared to the general lung cancer population. With that in mind, it is likely that, though a younger, fitter patient group (fewer co-morbidities), RET fusion positive patients may well be diagnosed later, as they do not fit the 'typical' lung cancer patient profile. .
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In recent years, we have seen new therapy options for some patients with Non Small Cell Lung Cancer – Target Therapies and Immunotherapies. There is, however, a need to identify further new targets and therapies for these groups. Selpercatinib, from January 2022, was made available, through the Cancer Drugs Fund, for patients with previously treated RET fusion positive non small cell lung cancer [NICE ID 3743]. In the untreated group, current systemic treatment would be with standard NSCLC treatment – a combination of chemotherapy and immunotherapy.

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?	Selpercatinib is the first therapy available specifically targeted at RET fusion positive lung cancer. Data presented shows this therapy has a 64% overall response rate in RET positive NSCLC patients previously treated with chemotherapy and 84% in those who received it as first line therapy. Selpercatinib is an oral preparation. In this time of COVID recovery, oral therapy has clear advantage over hospital requiring, intra-venous treatments.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The side effects associated with the therapy. We note the most common side effects reported included diarrhoea, high blood pressure, increased liver enzymes. Serious side effects included abnormal heart rhythms and pneumonia. In the study, most side effects were managed by dose reduction/interruption. Dosage interruption occurred in 42% of patients and dose reduction occurred in 31% of patients. However, 5% of patients stopped treatment due to side effects. This underlines the importance of management by a specialist lung cancer oncology team.

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?	As an oral therapy for a highly selected patient group, during these times of COVID, reducing hospital attendance for systemic therapy would be preferable.

Key messages

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

- First targeted therapy specifically being assessed for untreated RET positive lung cancer.
- Oral therapy.
- Perhaps consider availability through the Cancer Drugs Fund, in this indication, whilst further research is ongoing
-
-
-
-
-

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]

Professional organisation submission

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Royal College of Pathologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology. Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathology is a professional membership organisation, to maintain the standards and reputation of British pathology, through training, assessments, examinations, and professional development. It is a registered charity.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	I personally was paid £770 by Eli Lilly to attend an advisory board meeting on *RET* rearrangement testing in October 2021.
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 extend life and to improve quality of life in incurable disease
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	As a pathologist, I am not qualified to comment on this.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Patients with *RET*-positive lung cancers respond well to targeted treatment which is associated with high quality of life. At the moment, patients must endure chemotherapy/immunotherapy/both before being able to access targeted treatment; these alternative options are associated with more side effects than targeted treatment. In addition, there is good evidence to show that these patients do not derive benefit from immunotherapy. At the moment, it seems that patients must endure first-line chemotherapy/immunotherapy/both before they can receive the optimal treatment.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	First line chemotherapy, immunotherapy or combination immunotherapy/chemotherapy
9a. Are any clinical guidelines used in the	As a pathologist, I am not qualified to comment on this.

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.)	As a pathologist, I am not qualified to comment on this.
9c. What impact would the technology have on the current pathway of care?	There would be a requirement for RET rearrangement testing up-front in advanced non-small cell lung cancer. However, these patients already need (at least) EGFR mutation and ALK/ROS1 rearrangement testing up-front. Since the National Genomic Test Directory mandates the use of NGS panels, therefore, RET testing should already be being undertaken alongside these tests. For centres using NGS panel testing provided by Genomic Laboratory Hubs, therefore, the addition of a requirement for RET status up front should make no difference – it should already be provided at present – and will not delay results or require additional tumour tissue. Therefore, there should be no change for centres using Genomic Laboratory Hubs for testing. However, for centres which are performing targeted testing for EGFR, ALK and ROS1, the introduction of this technology would mandate another test up-front. Targeted testing approaches for RET are not as convenient as for ALK and ROS1. Therefore, for centres not using NGS panels provided by GLHs and who do not already request RET testing in first-line, the need for RET testing in first-line may lead to delays in providing the results required to decide on first-line treatment. This will also require the use of more tissue; for small biopsies, such a large amount of targeted testing may simply not be possible. Anecdotally, though, my experience is that even centres which do not request NGS panel testing from GLHs already tend to get RET testing done up-front. Therefore, I believe that the introduction of this technology would have an impact only on a few small minority of centres.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As a pathologist, I am not qualified to comment on this

10a. How does healthcare resource use differ between the technology and current care?	It will require that RET testing is undertaken up-front, rather than as a second-line test. This will have no resource implications for those centres requesting panel testing from GLHs. However, it may increase costs for centres which use targeted testing outside the GLH system, and which do not currently request RET testing in first line (anecdotally, I believe that this is not many centres).
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	As a pathologist, I am not qualified to comment on this
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	From a testing perspective, GLHs are already funded by NHS England to undertake RET testing. However, pathology departments are – as yet – not funded to prepare tumour tissue to send to GLHs (NHS England has not yet made a decision on this). This may limit the ability of pathology departments to provide these results in a timely fashion.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. As stated above, patients with RET-positive cancers currently must receive chemotherapy/immunotherapy/combination which is associated with considerably more side effects than targeted therapy. There is also now good evidence that RET-positive NSCLC respond poorly to immunotherapy. At the moment, it therefore feels like patients must endure less well tolerated (and potentially less effective) therapy, before they become eligible for their ideal therapy.
11a. Do you expect the technology to increase length of life more than current care?	As a pathologist, I am not qualified to comment on this
11b. Do you expect the technology to increase health-related quality of life more than current care?	As a pathologist, I am not qualified to comment on this
12. Are there any groups of people for whom the technology would be more or less effective (or	RET fusions are more common in patients with adenocarcinomas and in non-/light-smokers. These patients therefore stand to gain more than the general population of patients with lung cancer, but this is simply a reflection of the epidemiology of RET fusions.

appropriate) than the general population?	

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are 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.)	See above for notes on implications for testing. If centres already use NGS panel testing from GLHs for routine up-front profiling of lung cancers, there will be no impact from a resource perspective. Anecdotally, I believe that most centres which do not make use of NGS panels from GLHs already request RET testing as part of their up-front profiling of lung cancers. For these centres, there will be no impact from a resource perspective. For the small number of centres which do not already request RET testing up-front in lung cancers: ▪ The additional need for RET testing (if not undertaken as part of NGS panels through GLHs) will likely introduce a delay in making a decision to start first-line treatment and may simply not be possible with small biopsies. ▪ If these centres do choose to start sending their cases for NGS panel testing at GLHs, this will introduce an extra financial pressure on pathology departments in preparing tissue for GLH

	testing. NHS England is still to make a decision on providing funding for this work. Until that funding is provided, this extra work will likely delay tissue preparation and therefore will likely delay results.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As a pathologist, I am not qualified to comment on this
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	As a pathologist, I am not qualified to comment on this
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?	As a pathologist, I am not qualified to comment on this
16a. Is the technology a 'step-change' in the management of the condition?	Yes. RET-positive lung cancers are better served with targeted therapy from the beginning, rather than having to be treated with initial chemotherapy/immunotherapy/both.

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. We know that the most appropriate treatment for the subset of lung cancer patients with RET fusions (both in terms of tolerability and, in most cases, also efficacy) is targeted therapy, but patients are not able to access this treatment in first-line.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As a pathologist, I am not qualified to comment on this

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	As a pathologist, I am not qualified to comment on this
18a. If not, how could the results be extrapolated to the UK setting?	As a pathologist, I am not qualified to comment on this
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	As a pathologist, I am not qualified to comment on this
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	As a pathologist, I am not qualified to comment on this

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	As a pathologist, I am not qualified to comment on this
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	As a pathologist, I am not qualified to comment on this
20. How do data on real-world experience compare with the trial data?	As a pathologist, I am not qualified to comment on this

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not from a testing perspective. The GLH system in England and the All Wales Medical Genetics Laboratory provide equitable access to testing across England and Wales. However, in the absence of funding of pathology departments to prepare tissue for genomic testing, it is up to individual trusts to provide the funding for this work. Anecdotally, I know that some trusts are not able to fund this work – patients from these trusts do not have access to the comprehensive testing provided by GLHs and instead receive targeted testing which may or may not include RET. Until NHS England makes a decision on central funding for this work, there will continue to be inequity of access from one trust to another.
21b. Consider whether these issues are different from issues with current care and why.	The above largely applies to the current situation. The issue with this technology is that the results will be needed more quickly and, in the absence of central funding, there will be inequity from one trust to another in terms of how quickly they can prepare tissue for genomic testing.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Many centres already test for RET fusions up-front via the GLHs at diagnosis of NSCLC, and for these centres this technology would have no impact. • Most of the remaining centres already test for RET fusions up-front, but using targeted technologies outside the GLH system – for these centres, turnaround times for RET testing may delay first-line treatment. • A few centres do not currently test RET in first-line. For these centres there will be extra resource implications to this technology which will likely lead to delayed results. • In the absence of central funding for tissue preparation for genomic testing by pathology laboratories, RET testing will never be as quick as it could be. •

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC+)
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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Nigel Armstrong acted as project lead and health economist/review manager on this assessment, critiqued the clinical effectiveness methods and evidence and contributing to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Bram Ramaekers, Manuela Joore, Thomas Otten, Andrea Coves Fernandez and Teebah Abu-Zarah acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mark Perry acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Robert Wolff critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Abbreviations

ACTH	Adrenocorticotropic hormone
AE(s)	Adverse event(s)
AESI	Adverse event of special interest
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATEZ	Atezolizumab
BEV	Bevacizumab
BIC	Bayesian information criteria
BICR	Blinded Independent Committee Review
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
c	Continuous
CADTH	Canadian Agency for Drugs and Technologies in Health
CAMR	Camrelizumab
CARB	Carboplatin
CASP	Critical Appraisal Skills Programme
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CEA	Carcinoembryonic antigen
CEMIPL	Cemiplimab
CENTRAL	Cochrane Central Register of Controlled Trials
Cf-DNA	Circulating free DNA
CI	Confidence interval
CIS	Cisplatin
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CR	Complete response
CrI	Credible intervals
CS	Company submission
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
Dbar	Mean sum of residual deviances
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DURV	Durvalumab
ECG	Echocardiograms
ECOG	Eastern Cooperative Oncology Group
EAG	Evidence Assessment Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
eMIT	electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ	European Platform of Cancer Research Quality of Life Questionnaire

EORTC QLQ–C30	European Platform of Cancer Research Quality of Life Questionnaire core 30
EoT	End of treatment
EQ-5D	European Quality of Life-5 Dimensions
ERL	Erlotinib
EUR	Erasmus University Rotterdam
FE	Fixing errors
FV	Fixing violations
FISH	Fluorescence in-situ hybridisation
GEF	Gefitinib
GEM	Gemcitabine
HIV	Human immunodeficiency virus
HR(s)	Hazard ratio(s)
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Appraisal
i	Induction
IA	Investigator Assessment
IAS	Integrated Analysis Set
ICER(s)	Incremental cost-effectiveness ratio(s)
ICTRP	International Clinical Trials Registry Platform
ID	Identification
iNHB	incremental net health benefit
iNMB	incremental net monetary benefit
IPD	Individual patient data
IPI	Ipilimumab
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intention to treat
JAK	Janus kinase
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Limited
LPS	Lansky Performance Score
LTFU	Lost to follow-up
LY(s)	Life year(s)
M	Maintenance
MJ	Matters of judgement
MSI	Microsatellite instability
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
N	Number of patients
n	Number of patients in specific category
N/A	Not applicable
Nab-PAC	Nab-paclitaxel
NCI CTCAE	National Cancer Institute common terminology for AEs
NCT	National Clinical Trial
NE	Not estimable
NG122	NICE guideline 122
NGS	Next generation sequencing
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIVO	Nivolumab
NL	Netherlands
NMA	Network meta-analysis

NMB	Net monetary benefit
No	Number
NR	Not reported
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
ORR	Objective response rate
ORR	Overall response rate
OS	Overall survival
OSAS	Overall Safety Analysis Set
PAC	Paclitaxel
PAS	Primary Analysis Set
PAS	Patient Access Scheme
PCB	Placebo
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death 1 receptor
PD-L1	Programmed death receptor ligand 1
PEM	Pemetrexed
PEMBRO	Pembrolizumab
PF	Progression-free
PFLY(s)	Progression-free life year(s)
PFS	Progression-free survival
PK	Pharmacokinetic
PLAT	Platinum chemotherapy
PPI	Proton pump inhibitor
PR	Partial response
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSM	Propensity score matching
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PSW	Propensity score weighting
QALY(s)	Quality-adjusted life year(s)
QD	Once daily
QLQ	Quality of life questionnaire
QoL	Quality of life
OS	Overall survival
QT	QT interval
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RP2D	Recommended Phase II dose
RAM	Ramucirumab
RANO	Response assessment in neuro-oncology criteria
RBC	Red blood cell
RCT(s)	Randomised controlled trial(s)
RDI	Relative dose intensity
RE	Random-effects
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Rearranged during transfection
RMST	restricted mean survival time
RP2D	Recommended phase 2 dose
RT	Radiation therapy

RWE	Real world evidence
SAS	Safety Analysis Set
SAS	Supplemental Analysis Set
SAS1	Supplemental Analysis Set 1
SAS2	Supplemental Analysis Set 2
SAS3	Supplemental Analysis Set 3
SCE	Summary of Clinical Efficacy
SD	Standard deviation
SD	Stable disease
SEL	Selpercatinib
SFU	Safety follow-up
SINT	Sintilimab
SIREN	Selpercatinib in RET fusion-positive non-small-cell lung cancer
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
STM	State transition model
TA(s)	Technology Appraisal(s)
TEAE(s)	Treatment emergent adverse event(s)
TISL	Tislelizumab
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
UMC+	University Medical Center+
US	United States
WHO	World Health Organization
WTP	Willingness-to-pay

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues are related to the cost-effectiveness while a summary is in presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost-effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Sections
1	Population: uncertainty as to whether includes squamous histology for which no evidence has been provided.	2.1
2	Comparators: mismatch to NICE scope and NICE guideline, which might undermine the validity of any effectiveness or cost-effectiveness estimates.	2.2, 3 to 6
3	Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice.	3.2.4
4	Lack of comparative evidence in the correct population, which might mean treatment effect of selpercatinib overestimated and ICERs underestimated.	3
5	Applicability: there is the possibility of differences between trial and UK target population in race and CNS metastases (due to limited information). Combined with evidence of the possibility that race and CNS metastases are effect modifiers, this implies that results from the trial may not be applicable to the UK target population.	3.2.5.6
6	Adverse events: there are no specific adverse event data for the treatment naïve sub-set (SAS1 dataset) in LIBRETTO-001, or the equivalent subset of the LIBRETTO-321.	3.2.8
7	ITC: choice of trial data (KEYNOTE-189) might have biased comparison with all comparators.	3.4
8	ITC: methods of adjustment for confounding might have biased comparison with all comparators.	3.4
9	NMA: heterogeneity in trials to inform pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy.	3.4.2
10	No NMA or comparative analysis was carried out for adverse events, preventing a rigorous assessment of benefits and harms.	3.4.2.4
11	Lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties in the extrapolation period.	4.2.2 and 5.2

ID1457	Summary of issue	Report Sections
12	Immaturity of the data obtained from the LIBRETTO-001 trial for OS and PFS, adding substantial uncertainty to the extrapolated survival data in the economic model.	4.2.6
13	The company's choice of survival curves for the modelling of treatment effectiveness was not transparent.	4.2.6
14	Waning of the selpercatinib treatment effect was not explored.	4.2.6
15	Potential underestimation of PFS pemetrexed plus platinum chemotherapy and hence an overestimation of the increments versus selpercatinib.	4.2.6 and 5.1
16	Utility values were higher than the ones used in other TAs, only slightly lower than the UK general population, and had a relatively small decrement between PF and PD states.	4.2.8
17	The plausibility of the company's choices for the modelling of subsequent treatments.	4.2.9

ICERs = incremental cost-effectiveness ratios; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; OS = overall survival; PD = progressive disease; PF = progression-free; PFS = progression-free survival; PSM = propensity score matching; SAS1 = supplemental analysis set 1; STM = state transition model; UK = United Kingdom

1.2 Overview of key model outcomes

National Institute for Health and Care Excellence technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost per QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased progression-free survival (PFS) for selpercatinib (QALYs in the progression-free (PF) health state increased by [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively) and increased overall survival (OS) for selpercatinib (survival (undiscounted) increased by [redacted] and [redacted] years compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively). This resulted in post-progression benefits of [redacted] and [redacted] QALYs compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively (estimates retrieved from company submission (CS), Appendix J).
- Treatment benefit (in terms of OS and PFS) are maintained for the whole duration of the time horizon i.e., no waning of these treatment benefits.

Overall, the technology is modelled to affect costs by:

- The higher treatment costs (additional costs of [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively) and higher disease management costs (additional costs of [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively). These costs are partly offset by lower subsequent treatment costs (cost savings of [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively; estimates retrieved from CS, Appendix J).

The parameters that have the greatest effect on the ICER (based on the company's deterministic sensitivity analyses) were:

- Discount rate for costs
- Discount rate for outcomes
- Drug administration costs
- Subsequent active systemic anticancer therapy costs
- Drug related monitoring costs
- Adverse event costs

Based on the company's scenario analyses, modelling assumptions that have the greatest effect on the ICER were related to:

- Estimation of time to treatment discontinuation (TTD)
- Estimation of PFS
- Estimation of OS
- Subsequent therapy distribution
- Assuming alternative utility values (from TA654)

1.3 The decision problem: summary of the EAG's key issues

Table 1.2: Key issue 1: Population: uncertainty as to whether includes squamous histology for which no evidence has been provided

Report Section	**2.1**
Description of issue and why the EAG has identified it as important	No evidence was provided for the squamous population, but the company want the population for which NICE considers selpercatinib to include it. The FAC has also revealed that a license extension has been granted by the MHRA to include patients who have been previously treated, except with a RET inhibitor.[1] The EAG notes that the evidence that has been submitted was consistent with the scope in terms of patients being treatment naïve and not with the license extension.
What alternative approach has the EAG suggested?	The EAG would argue that the relevant population should only be non-squamous histology.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Evidence in the squamous population if it is to be included in a recommendation by NICE. Further evidence would need to be submitted if the scope was to be broadened to include patients who are not untreated.
EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence	

Table 1.3: Key issue 2: Comparators: mismatch to NICE scope and NICE guideline, which might undermine the validity of any effectiveness or cost-effectiveness estimates

Report Section	**2.2, 3 to 6**
Description of issue and why the EAG has identified it as important	Some comparators in the scope and which are recommended in the latest NICE guideline, NG122, are not included in the decision problem and thus the clinical effectiveness and cost-effectiveness analyses. The limited array of comparators in the decision problem (two) may have influenced interpretations. Had other comparators been present, as requested by the NICE scope,

Report Section	2.2, 3 to 6
	selpercatinib may not have emerged as the most effective and cost-effective treatment.
What alternative approach has the EAG suggested?	Include all comparators in the scope.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Provide evidence that the omitted comparators are not being used in NHS clinical practice or evidence of selpercatinib's clinical effectiveness and cost-effectiveness versus those comparators.
EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.4: Key issue 3: Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice

Report Section	3.1.2, 3.3, 3.4, and 4
Description of issue and why the EAG has identified it as important	There are discrepancies between the subsequent therapies used in the LIBRETTO-001 trial and clinical expert opinion as to UK clinical practice. In particular, percentage use in LIBRETTO-001 (numbers unclear) versus. assumed in clinical practice are: • pemetrexed plus platinum chemotherapy: very low in (precise number difficult to ascertain) versus. 70% • best supportive care: apparently none versus. 20% • pembrolizumab plus pemetrexed and platinum chemotherapy: [redacted] might have received pembrolizumab in some combination versus. 5%. This could lead to trial results that are not applicable to the target population.
What alternative approach has the EAG suggested?	Clarity as to the distribution of subsequent therapies in LIBRETTO-001. Costing in the economic model in line with the trial.
What is the expected effect on the cost-effectiveness estimates?	ICER probably underestimated either due to bias in effectiveness or cost.
What additional evidence or analyses might help to resolve this key issue?	Clarity as to the distribution of subsequent therapies in LIBRETTO-001. Costing in the economic model in line with the trial.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; UK = United Kingdom	

Table 1.5: Key issue 4: Lack of comparative evidence in the correct population, which might mean treatment effect of selpercatinib overestimated and ICERs underestimated

Report Section	3.1.2, 3.3, and 3.4
Description of issue and why the EAG has identified it as important	The submission relies on a single arm study of selpercatinib, LIBRETTO-001 compared via an ITC with a pemetrexed plus platinum chemotherapy single arm from another trial, KEYNOTE-189, and pembrolizumab with pemetrexed plus platinum chemotherapy via an NMA including KEYNOTE-189,

Report Section	3.1.2, 3.3, and 3.4
	-189 Japan and -021, all in a largely non-*RET* fusion-positive population. However, there is evidence, albeit of low quality, that the effectiveness of pemetrexed might be considerably higher in the RET fusion-positive population. Also, results for an RCT, LIBRETTO-431 versus both comparators in the decision problem in the RET fusion-positive population might be available during 2023.
What alternative approach has the EAG suggested?	Attempt to obtain comparator evidence in the RET fusion-positive population for the ITC and NMA.
What is the expected effect on the cost-effectiveness estimates?	ICER probably underestimated.
What additional evidence or analyses might help to resolve this key issue?	Attempt to obtain comparator evidence in the RET fusion-positive population for the ITC and NMA. Obtaining the RCT data is by far the best option.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; NMA = network meta-analysis; RCT = randomised controlled trial; RET = rearranged during transfection	

Table 1.6: Key issue 5: Applicability based on population characteristics: there is no information on the characteristics of UK target population

Report Section	3.1.2, 3.3, 3.4
Description of issue and why the EAG has identified it as important	The data showed similarities between a UK survey and the SAS1 trial dataset in age, but differences in sex, ECOG score and molecular assay type. Although the data on ethnicity were similar between the UK survey and the SAS1 trial dataset, these data did not differentiate between important ethnic groups in the UK. No data were provided for UK patients on history of metastatic disease. Meanwhile, the sub-group analyses demonstrated that any metastatic disease, CNS metastases, and age may be effect modifiers, and the incomplete sub-group analysis of 'race' means that 'race' cannot be excluded as an effect modifier. Whilst it is true that none of the results of the subgroup analysis were found to be statistically significant, a lack of statistical significance is not particularly informative in analyses that were not sufficiently powered, and the EAG believes that the point estimate differences are of sufficient magnitude to imply the possibility of type II errors. Therefore, the possibility that any metastatic disease, CNS metastases and race may differ between trial and target population (in the absence of adequate information) and the evidence that CNS metastases and race are possible effect modifiers make it possible that the effects in the trial may not be applicable to those that might be observed in the target population.
What alternative approach has the EAG suggested?	Provide characteristics of the UK target population.

Report Section	3.1.2, 3.3, 3.4
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Provide characteristics of the UK target population.
CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EAG = Evidence Assessment Group; UK = United Kingdom	

Table 1.7: Key issue 6: Adverse events: there are no specific adverse event data for the eligible participants relevant to the decision problem

Report Section	3.2.8
Description of issue and why the EAG has identified it as important	There are no specific adverse event data for the eligible participants relevant to the decision problem: the treatment naïve subset (SAS1 dataset) in LIBRETTO-001, or the equivalent subset of the LIBRETTO-321. This is a potential problem as it is it is not possible to exclude a greater concentration of adverse events in this subgroup than are observed overall.
What alternative approach has the EAG suggested?	Provide adverse events data specific to the eligible subsets.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Provide adverse events data specific to the eligible subsets.
EAG = Evidence Assessment Group; SAS = safety analysis set	

Table 1.8: Key issue 7: ITC: choice of trial data might have biased comparison with all comparators

Report Section	3.1.2, 3.3, 3.4
Description of issue and why the EAG has identified it as important	The company stated that the choice of trial (KEYNOTE-189) was determined by access to individual patient data, which permitted the best method of conducting the ITC. The choice of using the pemetrexed plus platinum chemotherapy data from the KEYNOTE-189 RCT as the pseudo-comparator arm is stated as being due to relevant IPD not being available from any other sources, which the EAG consider to be not a convincing rationale. It is likely that had other sources of pemetrexed plus platinum chemotherapy data been used, then very different overall NMA results might have been yielded.
What alternative approach has the EAG suggested?	Consider another source of individual patient data such as KEYNOTE-021.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Consider another source of individual patient data such as KEYNOTE-021.

Report Section	3.1.2, 3.3, 3.4
EAG = Evidence Assessment Group; ITC = indirect treatment comparison; NMA = network meta-analysis; RCT = randomised controlled trial	

Table 1.9: Key issue 8: ITC: methods of adjustment for confounding might have biased comparison with all comparators

Report Section	3.1.2, 3.3, 3.4
Description of issue and why the EAG has identified it as important	The methodology used for matching of the pseudo-comparator arm to the selpercatinib arm may not have been optimal. Of the methods explored, all of which had comparable baseline characteristic balance deficits, it appears that the default PSM method led to the most conservative results, which initially supports the presentation of results based upon this method. However, because the array of methods explored by the company were limited, it is possible that unexplored methods leading to a better degree of balance (such as addition of multivariate regression on the matched sample) might have yielded results that were less favourable to selpercatinib than those observed by the default PSM approach. It is also possible, given lack of rationale for choice of covariates, that important ones such as RET fusion status and brain metastases have been omitted.
What alternative approach has the EAG suggested?	Addition of multivariate regression on the matched sample. Consideration of other covariates and selecting only RET fusion-positive comparator patients.
What is the expected effect on the cost-effectiveness estimates?	ICER probably underestimated.
What additional evidence or analyses might help to resolve this key issue?	Addition of multivariate regression on the matched sample. Consideration of other covariates and selecting only RET fusion-positive comparator patients.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; PSM = propensity score matching; RET = rearranged during transfection	

Table 1.10: Key issue 9: NMA: heterogeneity in trials to inform pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy

Report Section	3.1.2, 3.3, 3.4
Description of issue and why the EAG has identified it as important	Possible differences between studies in ethnicity/clinical practice (KEYNOTE-189 Japan was comprised only of Japanese patients) suggest possible clinical heterogeneity across the three pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy trials. This is supported by large differences in point estimates across the three trials in both OS and PFS outcomes. Statistical heterogeneity for either outcome was not detected on I^2 testing. However, this may be a type II error, given that the study was not powered for such analyses, and in view of the clinical heterogeneity and the large point estimate differences. Another potential source of heterogeneity is RET fusion status. Although this does not seem to be available for any of the trials in the NMA, if it were for KEYNOTE-189 then the other two

Report Section	3.1.2, 3.3, 3.4
	trials could be excluded for the comparison with pembrolizumab plus pemetrexed plus platinum chemotherapy.
What alternative approach has the EAG suggested?	Re-analysis after removal of studies e.g., KEYNOTE-189 Japan.
What is the expected effect on the cost-effectiveness estimates?	ICER probably underestimated.
What additional evidence or analyses might help to resolve this key issue?	Re-analysis after removal of studies e.g., KEYNOTE-189 Japan.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; RET = rearranged during transfection	

Table 1.11: Key issue 10: No NMA or comparative analysis was carried out for adverse events

Report Section	3.1.2, 3.3, 3.4
Description of issue and why the EAG has identified it as important	No NMA or any kind of comparative analysis was carried out for adverse events, preventing a rigorous assessment of benefits and harms.
What alternative approach has the EAG suggested?	A comparison between selpercatinib and all comparators, including an NMA, should be added for adverse events.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	A comparison between selpercatinib and all comparators, including an NMA, should be added for adverse events.
EAG = Evidence Assessment Group; NMA = network meta-analysis	

1.5 The cost-effectiveness evidence : summary of the EAG's key issues

A full summary of the cost-effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost-effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The main EAG results are reproduced using confidential Patient Access Schemes (PAS) in a confidential appendix. The key issues in the cost-effectiveness evidence are discussed in the issue Tables below.

Table 1.12: Issue 11: Model structure

Report Section	4.2.2 and 5.2
Description of issue and why the EAG has identified it as important	NICE DSU TSD 19 recommends the use of state transition modelling to assist in verifying the plausibility of partitioned survival model extrapolations and to address uncertainties in the extrapolation period.
What alternative approach has the EAG suggested?	Compare the results of the partitioned survival model to the outcomes of a state transition model.

Report Section	4.2.2 and 5.2
What is the expected effect on the cost-effectiveness estimates?	According to the EAG there is considerable uncertainty related to the extrapolation of the PFS and OS endpoints in the selpercatinib arm. This uncertainty has a potentially substantial impact on the ICER as the large majority of gains in the economic model are accumulated beyond the observed data period.
What additional evidence or analyses might help to resolve this key issue?	Use of state transition modelling to assist in verifying the plausibility of partitioned survival model extrapolations
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NICE DSU TSD 19 = National Institute for Health and Clinical Excellence Decision Support Unit Technical Support Document 19; OS = overall survival; PFS = progression-free survival	

Table 1.13: Key issue 12: Immaturity of the data obtained from the LIBRETTO-001 trial for OS and PFS

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The data obtained from the LIBRETTO-001 trial for OS and PFS are immature, adding substantial uncertainty to the extrapolated survival data in the economic model.
What alternative approach has the EAG suggested?	To reflect the uncertainty due to data immaturity, and resulting ambiguity in choice of survival curves, the EAG conducted scenario analyses to find the range of results given plausible parametric survival curves.
What is the expected effect on the cost-effectiveness estimates?	The scenario analyses resulted in iNMB ranges of around £28.000 for both comparators: pembrolizumab combination therapy: £39,808 to £67,101, pemetrexed plus platinum chemotherapy: -£36,197 to -£8,192
What additional evidence or analyses might help to resolve this key issue?	Long-term PFS and OS data to reduce the uncertainty around the cost-effectiveness results.
EAG = Evidence Assessment Group; iNMB = incremental net monetary benefit; OS = overall survival; PFS = progression-free survival	

Table 1.14: Key issue 13: The company's choice of survival curves for the modelling of treatment effectiveness was not transparent

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The company's choice of survival curves for the modelling of treatment effectiveness was not transparent.
What alternative approach has the EAG suggested?	The EAG would like to receive more detail and justification concerning the choice of parametric survival curves.
What is the expected effect on the cost-effectiveness estimates?	Unknown.

What additional evidence or analyses might help to resolve this key issue?	The EAG would like to receive more detail concerning the choice of parametric survival curves. Specifically, the EAG would like to see more information about a) the choice of considering complex survival curves, b) the plots that were not provided in the clarification response c) the choice between survival curves in detail and d) the mismatch between reported PFS and OS values in the CS and values used in the economic model.
CS = company submission; EAG = Evidence Assessment Group; OS = overall survival; PFS = progression-free survival	

Table 1.15: Key issue 14: Waning of the selpercatinib treatment effect was not explored

Report Section	**4.2.6**
Description of issue and why the EAG has identified it as important	The company did not explore waning of the selpercatinib treatment effect in the submission.
What alternative approach has the EAG suggested?	Hazard ratio plots for PFS and OS versus time to assess hazard ratios of selpercatinib versus comparators over time. An updated model and scenario analyses to explore the impact of treatment waning into the model.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Hazard ratio plots for PFS and OS versus time to assess hazard ratios of selpercatinib versus comparators over time. An updated model and scenario analyses to explore the impact of treatment waning (kicking in at different time points) into the model.
EAG = Evidence Assessment Group; OS = overall survival; PFS = progression-free survival	

Table 1.16: Key issue 15: Company's estimated progression-free life years for pemetrexed plus platinum chemotherapy

Report Section	**4.2.6 and 5.1**
Description of issue and why the EAG has identified it as important	The observed PFS for pemetrexed plus platinum chemotherapy (based on a 1.0 year or 1.5-year time horizon) is larger than the modelled PFS based on a lifetime time horizon. This might suggest that PFS for pemetrexed plus platinum chemotherapy is underestimated and hence the increments versus selpercatinib potentially overestimated.
What alternative approach has the EAG suggested?	Alternative approaches to estimate PFS for pemetrexed plus platinum chemotherapy where the modelled PFS > observed PFS for pemetrexed plus platinum chemotherapy.
What is the expected effect on the cost-effectiveness estimates?	Based on the CS scenario analyses (as summarised in Section 5.2 of this report), PFS was amongst the modelling assumptions that have the greatest effect on the ICER.
What additional evidence or analyses	Long-term PFS data.

Report Section	4.2.6 and 5.1
might help to resolve this key issue?	
CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; PFS = progression-free survival	

Table 1.17: Key issue 16: Health-related quality of life

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	The utility values from the company's base-case were higher than the ones used in other TAs, only slightly lower than the age and gender matched UK general population and had a small decrement between PF and PD states.
What alternative approach has the EAG suggested?	The EAG requested scenario analyses exploring utility values from other relevant TAs. The EAG implemented the PD utility from TA654 in its base-case.
What is the expected effect on the cost-effectiveness estimates?	All provided scenario analyses including utility values from other TAs resulted in higher ICER than the company's base case. Implementing the PD utility from TA654 increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	N/A.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; PF = progression-free; PD = progressed disease; TA = Technology Appraisal; UK = United Kingdom	

Table 1.18: Key issue 17: Resources and costs

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	The plausibility of the company's choices for the modelling of subsequent treatments.
What alternative approach has the EAG suggested?	Informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial. Informing subsequent treatments for the comparators based on NG122 and expert oncologist inputs.
What is the expected effect on the cost-effectiveness estimates?	The EAG base-case approach slightly decreased the ICER versus pembrolizumab combination therapy and substantially increased the ICER versus pemetrexed plus platinum chemotherapy. The expected effect of informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial is unclear.
What additional evidence or analyses might help to resolve this key issue?	A scenario analysis informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NG122 = NICE guideline 122	

1.6 Summary of the EAG's view

The CS base-case probabilistic ICERs versus pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy were £5,209 and £36,025 per QALY gained, respectively. The estimated EAG base-case ICERs (probabilistic) versus pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy, based on the EAG preferred assumptions highlighted in Section 6.1, were £5,535 and £42,230 per QALY gained, respectively. The most influential adjustments were using the PD utility from TA654 and informing subsequent treatments based on NICE guideline 122 (NG122) and expert oncologist inputs. The ICER increased most in the scenario analyses with alternative assumptions regarding the modelling of PFS and OS.

In conclusion, there is large remaining uncertainty about the effectiveness and cost-effectiveness of selpercatinib, which can be partly resolved by the company by conducting further analyses. This includes providing outcomes of a state transition model (STM) to assist in verifying the plausibility of the propensity score matching (PSM) extrapolations, more transparency/details concerning the choice of parametric survival curves, scenario analyses exploring potential waning of the selpercatinib treatment effect, and a scenario analysis informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial. Mature long-term selpercatinib PFS and OS data would help to reduce the uncertainty surrounding the extrapolated survival data. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of selpercatinib compared with relevant comparators.

Table 1.19: Summary of EAG's preferred assumptions and ICER

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
CS base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,883	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,264	[redacted]	[redacted]
Fixing error (1-Error in calculation of total subsequent treatment costs)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,883	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,264	[redacted]	[redacted]
Fixing error (2-Inconsistency subsequent treatment after selpercatinib)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,662	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£4,987	[redacted]	[redacted]
Matter of judgement (3-PD utility based on TA654)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£38,478	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£6,859	[redacted]	[redacted]
Matter of judgement (4-Subsequent treatments based on NG122 and expert oncologist)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£40,467	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,347	[redacted]	[redacted]
Deterministic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,187	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,599	[redacted]	[redacted]
Probabilistic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,230	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,535	[redacted]	[redacted]

[1] ICER versus selpercatinib; [2] iNMB and iNHB for willingness-to-pay (WTP) of £36,000 per QALY
CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; iNMB = increment net monetary benefit; NG122 = NICE guideline 122; PD = progressed disease; QALY = quality adjusted life year; TA = Technology Appraisal

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with untreated advanced *RET* fusion-positive NSCLC.	Treatment-naïve patients with advanced non-squamous *RET* fusion-positive NSCLC who require systemic therapy.	The evidence presented in this submission is for patients with non-squamous histology. This population is in line with the LIBRETTO-001 Phase 1/2 trial (the clinical trial comprising the clinical evidence base for selpercatinib in the submission), where no treatment-naïve patients in the LIBRETTO-001 trial had squamous histology. RET fusions rarely occur in NSCLC tumours with squamous histology, which was acknowledged by the Committee in the previous evaluation for selpercatinib.	No evidence has been presented for patients with squamous histology, so the clinical effectiveness and cost-effectiveness in this subgroup is unknown.
Intervention	Selpercatinib	Selpercatinib 160 mg BID.	As per the NICE final scope.	The intervention is in line with the NICE scope.
Comparator(s)	For people with untreated advanced RET fusion positive NSCLC: • Pralsetinib (subject to ongoing NICE appraisal ID3875) For people with non-squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy	Pembrolizumab with pemetrexed and platinum chemotherapy. Pemetrexed and platinum chemotherapy.	As discussed above, the target population has been restricted to patients with non-squamous histology, in line with the population of the LIBRETTO-001 study. As a result, comparators presented in the pre-invitation scope relevant to the squamous population will not be included in the submission. This approach was discussed and accepted by the Committee for the selpercatinib	The company argue that the excluded comparators (pembrolizumab monotherapy, atezolizumab monotherapy, atezolizumab plus bevacizumab, carboplatin and paclitaxel and platinum doublet chemotherapy with or without pemetrexed maintenance treatment) are not used frequently enough according to clinical expert

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) with or without pemetrexed maintenance treatment For people with adenocarcinoma or large-cell carcinoma whose tumours express PD-L1 with a tumour proportion score below 50%: • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) with (following cisplatin-containing regimens only) or		evaluation for pre-treated NSCLC patients. In line with clinical experts consulted as part of the recent evaluation of pralsetinib in the same indication, feedback from UK clinical experts consulted by Eli Lilly as part of the evaluation process indicated that, of treatments available for patients with untreated, advanced, non-squamous NSCLC, patients with a positive *RET* status are most commonly treated with either pemetrexed with platinum-based chemotherapy OR pembrolizumab plus pemetrexed with platinum-based chemotherapy. As such, these are the only comparators considered relevant to this submission. Pralsetinib is not considered a relevant comparator in this population as it has not received a positive recommendation from NICE, and therefore is not considered part of routine practice.	opinion. This is despite these treatments being recommended by the NICE guideline NG122. A stronger rationale is required for a decision that could have a profound effect on clinical and cost-effectiveness.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	without pemetrexed maintenance treatment For people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab monotherapy • Atezolizumab • Pembrolizumab with carboplatin and paclitaxel (who need urgent clinical intervention) For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab with carboplatin and paclitaxel			
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rate • TTD	Primary: • ORR Secondary: • DOR • PFS • OS	As per the NICE final scope.	The outcomes reported are in line with the NICE scope apart from the addition of DOR.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment

	• Adverse effects of treatment
	• HRQoL.
		• Time to treatment discontinuation
		• HRQoL:
		  • EORTC QLQ-C30
		• Safety outcomes:
		  • AEs		

Economic analysis	The cost-effectiveness of treatments is expressed in terms of incremental cost per QALY. The time horizon for estimating cost-effectiveness was set at a lifetime horizon to sufficiently reflect any differences in costs or outcomes between the technologies being compared. Costs are considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	A cost-effectiveness analysis has been conducted for selpercatinib versus relevant comparators. As per the NICE reference case, cost-effectiveness is expressed in terms of incremental cost per QALYs. Costs are considered from the perspective of the NHS and PSS. A lifetime horizon is used to capture all costs and benefits associated with selpercatinib and its comparators.	In line with the NICE final scope.	Consistent with the scope.
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • tumour histology (squamous or non-squamous), and	The following subgroup analysis are considered: Subgroups analyses in *RET* fusion-positive advanced	PD-L1 status was not collected in the pivotal LIBRETTO-001 trial, therefore subgroup analyses of patients based on PD-L1 expression were not able to be performed. In addition, as all treatment-naïve patients with advanced	The EAG accepts the lack of feasibility of PD-L1 and tumour histology subgroup analysis, notwithstanding the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• level of PD-L1 expression.	NSCLC patients with brain metastases.	*RET* fusion-positive NSCLC enrolled in the LIBRETTO-001 trial had non-squamous histology, subgroup analyses by tumour histology were similarly not able to be performed. Subgroup analyses were conducted in patients with brain metastases. It has been found that approximately 50% of patients with *RET* fusion-positive NSCLC experience brain metastases therefore subgroup analyses in this population were performed.[2]	evidence being entirely in the non-squamous population. The EAG also considers that the brain metastases subgroup analysis might provide some evidence to suggest brain metastases should have been considered as a treatment effect modifier.

Based on Table 1 of the CS[3]

AEs = adverse events; BID = twice daily; CS = company submission; DOR = duration of response; EAG = Evidence Assessment Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire core 30; HRQoL = health-related quality of life; N/A = not applicable; NG122 = NICE guidelines 122; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PAS = Patient Access Scheme; PD-L1 = programmed death receptor ligand 1; PFS = progression-free survival; PSS = Personal Social Services; QALY = quality-adjusted life year; RET = rearranged during transfection; TTD = time to treatment discontinuation

2.1 Population

The population defined in the scope is: *"Adults with untreated advanced RET fusion-positive non-small cell lung cancer (NSCLC)"*.[4] The population in the company submission[3] (CS) is limited to *"Treatment-naïve patients with advanced non-squamous RET fusion-positive NSCLC who require systemic therapy".*

EAG comment:

- The phrase "who require systemic therapy" is added to the definition of the scope population in the company's decision problem (Table 2.1). Therefore, the Evidence Assessment Group (EAG) asked for the implications that this might have for the characteristics of the patients and standard care i.e., comparators as well as how would those who require systemic therapy be differentiated from those who do not. In response to the clarification letter the company stated that *"This wording was added to reflect the anticipated marketing authorisation for the indication under appraisal. Lilly can now confirm that the description of the population in the decision problem should be updated to align with the anticipated label: 'Selpercatinib as a monotherapy is indicated for the treatment of adults with advanced RET fusion-positive NSCLC not previously treated with a RET inhibitor'….As outlined in Section B.1.2.2. of the Company Submission, RET-fusion positive patients are identified via genetic testing. Specifically, next generation sequencing (NGS) can be completed by Genomics Hubs, which allows a panel of genetic mutations, rearrangements and fusions (including RET fusions) to be identified". The EAG interprets this response to mean that the phrase, "who require systemic therapy"* is no longer part of the definition of the population.
- The company stated that *"The evidence presented in this submission is for patients with non-squamous histology"* (Table 2.1). In the clarification letter, the EAG asked if the company could confirm that the population in the decision problem should be amended accordingly, to which the company responded as follows: *"As noted in Section B.1.2.1 of the Company submission, RET fusions are most commonly seen in adenocarcinoma, but have also been reported in mixed adenosquamous histology. The relative rarity of RET mutations with a squamous histology is supported by a recent retrospective observational study published by Hess 2021, which found that patients exhibiting metastatic NSCLC with RET mutations were more likely to have non-squamous histology than the general NSCLC population. As such, whilst squamous histology was not an exclusion criterion for enrolment in the LIBRETTO-001 trial, owing to the rarity of RET-fusion positive squamous histology, no squamous patients were enrolled into the SAS1 population. This is reflected by the Committee conclusions in a recent NICE appraisal, TA760 for selpercatinib in previously treated RET fusion-positive advanced NSCLC. In this submission, no evidence on the treatment of squamous tumours was presented owing to only a very small number of squamous patients enrolling in the efficacy set. However, the NICE Committee noted that the marketing authorisation for selpercatinib in this indication does not differentiate between patients with squamous and non-squamous histology. Furthermore, the Committee acknowledged that the RET-fusions positive squamous population is very small, and heard from clinical experts that the NHS would expect to follow the same recommendation for people with squamous advanced NSCLC as for people with non-squamous advanced NSCLC. As such, the Committee agreed that the recommendations would apply to both squamous and non-squamous advanced NSCLC. Therefore, Lilly can confirm that a broad recommendation, unrestricted by squamous histology, is being sought for selpercatinib in the first-line setting, and therefore that the population in the decision problem should not be amended from the wording currently provided".* Notwithstanding the advice from clinical experts, the EAG does not think it is ideal that recommendations are applied to

populations other than those on whom selpercatinib has been trialled and therefore this is a key issue.

- The company have not provided any comparative evidence, including via an indirect treatment comparison (ITC) or network meta-analysis (NMA), in the rearranged during transfection (RET) fusion-positive population.[3] Nor did they adjust for RET fusion status in the ITC (see Section 3.4.1). However, there is a randomised controlled trial (RCT) with a comparison to the two comparators in the decision problem in process (see Section 3.2.8). Therefore, lack of comparative evidence in the index population constitutes a key issue.

2.2 Intervention

The intervention is selpercatinib 160 mg twice daily (BID).

EAG comment: The intervention is in line with the scope.

2.3 Comparators

The comparators listed in the scope [4] are specified by histology, non-squamous or adenocarcinoma, and programmed death receptor ligand 1 (PD-L1) status. However, the company only lists two comparators, regardless of histology and PD-L1 status:

- pembrolizumab with pemetrexed and platinum chemotherapy
- pemetrexed and platinum chemotherapy

EAG comment:

- Pembrolizumab monotherapy, atezolizumab monotherapy, atezolizumab plus bevacizumab, carboplatin and paclitaxel and platinum doublet chemotherapy with or without pemetrexed maintenance treatment were not included as comparators, although they were all included in the scope, as well as the NG122 care pathway. Therefore, the EAG requested adequate justification for these discrepancies, citing objective evidence of standard care for the non-squamous advanced NSCLC population. In response to the clarification letter the company stated that, "*Pemetrexed with platinum chemotherapy is included in the NICE scope for patients with non-squamous histology. 'Pemetrexed in combination with a platinum drug (carboplatin or cisplatin)' is included in the list of comparators for patients with adenocarcinoma. As outlined in Section B.1.2.1 of the Company Submission, adenocarcinoma and large cell undifferentiated carcinoma are considered together under "non-squamous" histology. As outlined in Section B.1.2.2 of the Company Submission, comparator choice was informed by feedback received from expert oncologists practicing in the NHS to ensure only the most relevant comparators to selpercatinib in UK clinical practice were selected. The expert oncologist consulted noted that immunotherapies alone are less effective in RET-fusion positive patients and therefore their use in clinical practice is limited. The limited efficacy of mono-immunotherapy in these patients is supported by the conclusions of a real-world evidence study conducted by Offin et al. in 2019, which found median PFS in RET-fusion positive NSCLC patients treated with mono-immunotherapy was just 3.4 months (95% CI, 2.1 to 5.6 months). The authors concluded that RET-fusion positive lung cancers may be less likely to be highly responsive to immunotherapy as compared with other cancers, and noted that this was reflected in the overall poor outcomes observed. In addition to this, the expert oncologist consulted by Lilly emphasised that UK clinicians are typically keen to avoid use of mono-immunotherapies as first line options in RET-fusion positive patients, particularly considering the associated toxicities that can occur if a tyrosine kinase inhibitor (TKI) is subsequently provided in the second line. Based on this, the expert feedback received from Lilly was that patients in UK clinical practice*

are typically treated with either pemetrexed with platinum-based chemotherapy or pembrolizumab in combination with pemetrexed plus platinum chemotherapy, as these have demonstrated improved efficacy in the RET fusion-positive population. This feedback, and the subsequent comparator choice, is aligned with that received from clinical experts consulted as part of the recent evaluation of pralsetinib in the same indication (TA812). As such, pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy are considered the only relevant comparators to selpercatinib in this indication". The EAG also asked the company to conduct all effectiveness analyses, whether by ITC (by using individual patient data (IPD)) or NMA or combination (as in the CS), and cost-effectiveness analyses including all comparators in the scope and the NG122 care pathway. The company replied that, "*Lilly consider that pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy represent the only relevant comparators to selpercatinib in this submission. As such, neither an NMA nor cost-effectiveness analysis including the other treatments named in the NICE scope have been conducted".* The EAG is not satisfied with this response. The company have rejected NICE-recommended comparators based on clinical opinion and an arbitrary selection of evidence.

- A better approach would be to have included all the NICE scope comparators and tested the relative efficacy rigorously. In fact, the company have included the trial used to inform the NICE appraisal of atezolizumab plus bevacizumab, carboplatin and paclitaxel (Technology Appraisal (TA) 584) cited in NG122, IMPower 150, in the NMA (see Section 3.3), but not provided any results from this comparison.[5] The trials used to inform the NICE appraisals of pembrolizumab monotherapy (TA531)[6] and atezolizumab monotherapy (TA705)[7] cited in NG122, KEYNOTE-024 and IMPower 110 respectively were excluded from the NMA because "*Included PD-L1 ≥50% data only*" (see Table 28 in Appendix D).[8] There is no NICE appraisal associated with platinum doublet chemotherapy, but four trials of paclitaxel plus platinum induction are included in the NMA, all by comparison with the addition of bevacizumab and then via a connection to pemetrexed plus platinum chemotherapy (see network diagrams in Section 3.4). Any effectiveness estimate based on the NMA would probably then have to be adjusted based on the effect of the addition of maintenance pemetrexed, which is included in NG122 based on TA190.[9] The possibility therefore remains that there exist comparators that are either more effective than and/or cost effective versus selpercatinib and therefore this remains a key issue.

2.4 Outcomes

The NICE final scope[4] lists the following outcome measures (company decision problem in brackets):

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rate (overall response rate (ORR))
- Time to treatment discontinuation (TTD)
- Adverse effects of treatment
- Health-related quality of life (HRQoL) (European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C-30 (QLQ-C30))

The company also added duration of response (DOR).

EAG comment:

- In the clarification letter, the company were requested to explain the choice of HRQoL and the fact that European Quality of Life-5 Dimensions (EQ-5D) was not included, to which they responded, *"The phase I/II LIBRETTO-001 study collected EORTC QLQ-C30 data to address an exploratory*

objective: 'To collect patient-reported outcomes (PRO) data to explore disease-related symptoms and health-related quality of life (HRQoL)'. The study population was not restricted to one tumour type, like NSCLC, where more specific questionnaires would be available. EORTC QLQ-C30 is well established cancer PRO tool that is broadly used and validated, and it represents one of the most commonly used measures in cancer. As such, Lilly consider the EORTC QLQ-C30 data adequately and appropriately capture HRQoL for patients in the LIBRETTO-001 trial…. Generic measures of health, such as EQ-5D, are available and can be used to inform economic evaluation. However, they have been found to be inappropriate or insensitive for some medical conditions and for cancer in particular where it is less sensitive to cancer-specific symptoms. In contrast, as outlined in response to Part a) of this question, changes from baseline in disease-related symptoms and HRQoL are well addressed by the EORTC QLQ-C30. In addition, the LIBRETTO-001 study was a Phase I/II exploratory basket trial, including other solid tumours and was therefore not designed as a randomised trial or large confirmatory trial, such as those for Phase 3. As such, collection of EQ-5D data was not included in the trial design in order to lessen the burden of data reporting for health care providers and patients. However, the LIBRETTO-431 study uses more questionaries including both EORTC QLQ-C30 and EQ-5D". In view of this response, the EAG agrees that the use of EORTC QLQ-C30 in the trials was appropriate. However, the company's argument that EQ-5D was not used due to its lower sensitivity to cancer-specific symptoms is rather undermined by the fact that EQ-5D has been used in LIBRETTO-431.

- The company were also requested to justify the use of the outcome 'duration of response', given that this is not in the NICE scope and that it may overlap with other outcomes. The company responded by stating that, *"Overall response rate (ORR) was the primary endpoint in LIBRETTO-001, with objective response rate and best overall response also being measured. Improved response rate and reductions in tumour size may lead to the relief of symptoms and help to preserve HRQoL. Therefore, duration of response was also considered as an important outcome because by maintaining the response of the tumour to treatment and inducing shrinkage, relief from disease progression may be maintained for longer and patients may experience improved OS. However, results for this outcome were provided as supportive data only and did not inform the economic model"*. Given that duration of response does not inform the economic model, the EAG will not present results relating to 'duration of response' in this report.

2.5 Other relevant factors

None.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

A systematic literature search was conducted to identify clinical trial evidence on the efficacy and safety of selpercatinib and relevant comparators in untreated patients with NSCLC. Full details of the search strategies, study selection process and results were reported in Appendix D.[8]

3.1.1 Searches

The following section contains a summary and critique of literature searches related to clinical efficacy and safety presented in the CS.[3, 8] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[10, 11] The CS was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[12]

Appendix D of the CS provided details of the literature searches conducted for the systematic literature review (SLR) of clinical efficacy and safety.[8] The searches were conducted in January 2016 (SLR1), then updated in June 2018 (SLR2), July 2020 (SLR3), July 2021 (SLR4) and April 2022 (SLR5). Two additional searches were conducted to incorporate new comparator interventions in June 2018 (SLR2: additional comparators) and August 2020 (SLR3b). The additional comparator interventions were then included in subsequent update searches. A summary of the resources searched is provided in Table 3.1.

Table 3.1: Resources searched for the clinical effectiveness systematic review (as reported in the company submission).

Resource	Host/Source	Date Ranges		Dates searched	
Electronic databases					
MEDLINE and MEDLINE In-Process, E-Pub Ahead of Print	Ovid	SLR1 SLR2 SLR2 targeted SLR3 SLR3b SLR4 SLR5	Not reported Not reported Not reported Not reported Not reported Not reported Not reported	SLR1 SLR2 SLR2T SLR3 SLR3b SLR4 SLR5	12/01/2016 13/06/2018 13/06/2018 29/07/2020 27/08/2020 30/07/2021 20/04/2022
Embase	Ovid	SLR1 SLR2 SLR2 targeted SLR3 SLR3b SLR4 SLR5	Not reported Not reported Not reported Not reported Not reported Not reported Not reported	SLR1 SLR2 SLR2T SLR3 SLR3b SLR4 SLR5	12/01/2016 15/06/2018 15/06/2018 29/07/2020 27/08/2020 30/07/2021 20/04/2022
Evidence-based medicine reviews (Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of	Not reported	SLR1 SLR2 SLR3 SLR3b SLR4 SLR5	Not reported Not reported Not reported Not reported Not reported Not reported	SLR1 SLR2 SLR3 SLR3b SLR4 SLR5	12/01/2016 18/06/2018 30/07/2020 27/08/2020 30/07/2021 20/04/2022

Resource	Host/Source	Date Ranges	Dates searched
Reviews of Effects, Cochrane Clinical Answers, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, NHS Economic Evaluation Database)			
Clinical trials registries			
ClinicalTrials.gov		Not reported	Not reported
International Clinical Trials Registry Platform		Not reported	Not reported
Conference proceedings			
American Association for Cancer Research (AACR)	Embase (Ovid) AACR website	SLR2 2014 –Q2 2022 SLR3-SLR5	SLR2 23/07/2018 June 18-April 2022
The European Lung Cancer Conference (ELCC)	Embase (Ovid) Embase (Ovid) ELCC website	SLR1 2014 –Q2 2022 SLR2 2014 –Q2 2022 SLR3-SLR5	SLR1 25/01/2016 SLR2 23/07/2018 June 18-April 2022
World Conference on Lung Cancer (WCLC)	Embase (Ovid) Embase (Ovid) WCLC website	SLR1 2014 –Q2 2022 SLR2 2014 –Q2 2022 SLR3-SLR5	SLR1 25/01/2016 SLR2 23/07/2018 June 18-April 2022
European Society for Medical Oncology (ESMO)	Embase (Ovid) Embase (Ovid) ESMO website	SLR1 2014 –Q2 2022 SLR2 2014 –Q2 2022 SLR3-SLR5	SLR1 25/01/2016 SLR2 23/07/2018 June 18-April 2022
ESMO Immuno Oncology Congress	Embase (Ovid)	SLR2 2014 –Q2 2022	SLR2 23/07/2018
American Society for Clinical Oncology (ASCO)	Embase (Ovid) Embase (Ovid) ASCO website	SLR1 2014 –Q2 2022 SLR2 2014 –Q2 2022SLR3-SLR5	SLR1 25/01/2016 SLR2 23/07/2018 June 18-April 2022
HTA organisation websites			
National Institute for Health and Care Excellence (NICE)		Not reported	Not reported
Reference lists of any identified systematic reviews and meta-analyses published in the last year were searched for further studies of interest.			

EAG comment:

- The CS provided details of the literature searches for the EAG to appraise.[3, 8]

- A good range of databases and relevant conference proceedings were searched.
- Full details of the database search strategies, including the database name, host platform, and date searched, were provided. The database date ranges were not reported.
- Details of the conference proceedings searched were provided. The search terms used, URL links, specific date of searches, and results, were reported.
- The NICE website was searched for published assessments and guidelines. Full details of this search were not provided: search date, search terms, and number of records retrieved. Full details of the NICE website search were provided in response to the EAG clarification letter.[13]
- The clinical trials registries www.ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) were searched to identify ongoing clinical trials. Keywords were reported, but there were no details of the date searched and the number of records retrieved. Details of the dates searched for SLR4 and SLR5 were provided in the response to clarification.[13]
- The database search strategies were well structured, transparent and reproducible. They included truncation, proximity operators, synonyms, and subject headings (MeSH and EMTREE). There were no language or date limits.
- It would have been preferable for the database search strategies to be presented exactly as run, rather than copied into a tabular format, as item 8 of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-S reporting checklist recommends.[14] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[15]
- Study design search filters for RCTs were included in the search strategies. The search filters used were not cited, as current practice recommends.[14] It was not clear if the RCT filters were validated published filters or were devised by the review team.
- Separate searches for safety were not conducted. It is unlikely that efficacy searches that include study design filters for RCTs will be sensitive enough to identify safety data. Ideally, searches for adverse events should be carried out alongside efficacy searches.[16]
- The original Embase clinical evidence search strategy SLR1, and updates SLR2 and SLR3 were more precise than the equivalent MEDLINE search strategies, using focussed EMTREE, searching in the title field only, and using the frequency operator to search the abstract field.
- Two targeted searches were conducted (SLR2 targeted and SLR3b) when new comparator drugs were introduced to the search strategies.
- The SLR3b MEDLINE search strategy reported in Table 5 was incorrect, replicating the MEDLINE SLR3 strategy reported in Table 4. The strategy was correctly reported in Table 6.
- The MEDLINE, Embase and EBMR search strategies for the final two update searches (SLR4 and SLR5) were different to those search strategies used for the original searches and previous update searches (SLR1, SLR2, SLR2: targeted, SLR3 and SLR3b). Consequently, these final two searches were not updates, but rather 'new' searches.
- The Population search facet in the SLR4 and SLR5 searches was more precise than that used in the original search, which searched broadly for NSCLC. The more precise Population facet searched for NSCLC combined with search terms for 'advanced/metastatic' AND 'first line therapy'. Another element of the search strategy included a Population facet with additional search terms for 'RET fusion'.

- In the methods Section (see Appendix D.1.1) it was reported that '*search strategies did not specify treatment line'*, but the SLR4 and SLR5 update searches did include a search line for 'first line treatment' in the Population facet.[8]
- The SLR4 and SLR5 update searches included an age limit for 'Adults' that was not included in the previous searches.
- Different RCT filters were used in the SLR4 and SLR5 search strategies to those used in the original SLR1 search strategies (and updates, SLR2 and SLR3), and as the filters were not cited, it was not clear where they were derived from.
- In response to clarification questions about the differences in the search strategies used for SLR4 and SLR5, as listed above, the company explained that *'SLR1 and SLR2 were conducted from a Global perspective, with objectives and scope broader than the current decision problem. From SLR3, the search strategy was narrowed to make it more robust and specific; the addition of the search terms and age limits reduced the number of irrelevant hits produced. Fundamentally, the search strategy remained broadly similar throughout all of the relevant updates, but with amendments made for the last two updates to make them specific, directed and optimised for the population of interest. Lilly do not consider that these adjustments will have excluded any relevant data from the search results.'*[13]
- There were two elements to the SLR4 and SLR5 search strategies with separate results. One of the elements combined the search facets for Population, Interventions and RCT filter, but incorrectly only included search line #52 (the first line of the RCT filter), rather than search line #54 (the complete RCT filter) (Table 7, Table 8, Table 14 and Table 15).
- The date limit field tag 'date created (dc)' was used in the SLR4 and SLR5 update searches in MEDLINE and Embase, when it is only available in Embase; the equivalent field in MEDLINE is 'entry date (ed)'.
- The search line for 'first line/untreated therapy' was suboptimal, as it did not include truncation, proximity operators, and a number of the search terms were redundant.
- EBMR includes several different resources, but the CS only reported the results of searches from the Cochrane Central Register of Controlled Trials (CENTRAL).
- The host interface for EBMR was not reported. Although not reported, it appears that the SLR1 and SLR2 EBMR search strategies (Table 16 and Table 17) were conducted via the Cochrane Library, rather than via EBMR in Ovid. Search strategies for SLR3, SLR4 and SLR5 were conducted via Ovid EBMR.
- The EBMR search strategy for SLR3 was reported incorrectly, presenting duplicate search lines, and inaccurate set combinations (Table 18).
- The MEDLINE, Embase and EBMR search strategies for the final two update searches (SLR4 and SLR5) were identical, incorrectly using MeSH in Embase and EBMR.
- As the same search strategy was used for the SLR4 and SLR5 update searches in MEDLINE, Embase and EBMR, the RCT filter was included in the CENTRAL search. It is not necessary to include an RCT filter when searching a database of trials, as this may result in unnecessarily restricting the results retrieved.
- The last 40 search lines from line #24 onward were missing from the MEDLINE SLR5 search strategy (Table 8). The full MEDLINE SLR5 search strategy was provided in response to the EAG clarification letter.[13]

3.1.2 Inclusion criteria

A SLR was conducted to identify relevant clinical evidence on the efficacy and safety of treatments for advanced RET fusion-positive NSCLC who require systemic therapy, including treatment-naïve adults.

The original SLR was conducted in January 2016, and there were four subsequent updates in June 2018, July 2020, July 2021 and April 2022. The eligibility criteria used in the decisions for inclusion/exclusion into the SLR are presented in Table 3.2. For brevity this shall also be referred to as the SLR 'protocol' in the report.

Table 3.2: Eligibility criteria (protocol) used for selection of evidence for the company's SLR

Study characteristics	Eligible	Ineligible
Population	Adult patients (≥18 years old) with locally advanced or metastatic non-squamous NSCLC (stage IIIB or IV) receiving first line and first line to progression	Children and adolescents
Intervention	Selpercatinib (Loxo-292) Pralsetinib (Blu667) Afatinib Bevacizumab Carboplatin Cisplatin Crizotinib Docetaxel Erlotinib Gefitinib Gemcitabine Nab-Paclitaxel Nivolumab Paclitaxel Pembrolizumab Pemetrexed Ramucirumab Atezolizumab Durvalumab Ipilimumab Tremelimumab Combinations of the above.	Studies that do not include any of the interventions of interest in at least one study arm. Studies comparing an intervention of interest with nonpharmacological treatments e.g., surgery, complementary therapy.
Comparators	Any active systemic therapy, placebo, best supportive care, or no treatment.	Studies comparing an intervention of interest with non-pharmacological treatments e.g., surgery, complementary therapy.
Outcomes	At least one of the following outcomes: • PFS • OS • Safety (Grade 3–4 AEs)	Studies that do not report at least one of the outcomes of interest
Study Design	RCT[b] in first-line NSCLC. Language restriction to English. Systematic reviews.	Single-arm trials in patients without RET alterations. Prospective observational studies. Preclinical studies. Prognostic studies.

Study characteristics	Eligible	Ineligible
		Case reports. Commentaries and letters (publication type). Consensus reports. Non-systematic reviews. Registry studies. Case-control studies. Cross-sectional surveys. Retrospective studies.
Time frame	SLR1: Database inception to 12 January 2016 SLR2: 2016 to 13 June 2018 SLR3: 2018 to 29 July 2020[c] SLR4: 2020 to 30 July 2021 SLR5: 30 July 2021 to 20 April 2022[d]	None
Other considerations	Studies that included head-to-head comparisons of at least two of the treatments listed (or placebo) were eligible for inclusion.	Studies of monotherapies were not considered for inclusion.

Based on Table 25, CS Appendix D[8]
[a] Studies including only a mutation positive-specific population (EGFR+, ALK+) were excluded.
[b] RCTs with mixed histologic populations were included when results specifically for the non-squamous population were reported, an exception was made for CHECKMATE 227, KEYNOTE-042 and KEYNOTE-024 where efficacy data for squamous population were extracted.
[c] Additional search strategy to identify selpercatinib and pralsetinib (not in scope for the SLR1 or SLR2) was run on 27 August 2020 (SLR3b).
[d] Due to search string constraints in the EMBR databases, the time frame for EBMR will be restricted to January 2021-present in the searches.
AE = adverse events; ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial; RET = rearranged during transfection; SLR = systematic literature review.

EAG comment:

- The SLR protocol (Table 3.2) only appeared to include RCTs as the source of primary research findings, even though the company's own research work on selpercatinib (LIBRETTO-001 and LIBRETTO-321) did not involve RCT data. In the context of the CS,[3] a major purpose of the SLR is to ensure that all relevant data have been found and are available for inclusion in the clinical effectiveness section of the CS.[3] However, given the protocol wording, it would not seem possible for the LIBRETTO one-arm trials to be included in the SLR, and thus the clinical effectiveness Section.
- As a means to circumvent this, the company states in CS, Appendix D[8] that, '*Data in patient populations with RET fusions were expected to be sparse and therefore, single-arm trials reporting data from patients with RET fusion-positive NSCLC and data from RCTs in the wider non-squamous NSCLC population were also searched for.*' However, because this statement is not included in the protocol itself (Table 3.1) the rigour of the protocol as a pre-hoc determination of the scope and methodology of the SLR is called into question.

- As a further example, the dates of the four SLR updates are given, but no information is given on the nature of these updates. It is unclear if these updates were simply 're-runs' or if changes were made to the inclusion/exclusion criteria of the protocol on each update.
- In Section B.2.1 of the CS[3] the company stated that they included only "first-line to progression studies". The justification for this in Appendix D Section D1.1[8] is that selpercatinib is administered *"…until progression (or unacceptable toxicity)".* The company were asked to explain why the method in which selpercatinib is administered should determine the inclusion of studies of comparator treatments. The company stated that, "*As it is anticipated that selpercatinib will be administered 'until progression or until acceptable toxicity occurs' in UK clinical practice, the first line to progression treatment setting aligns more closely with the decision problem. In all studies categorised as "first line", the maximum number of treatment cycles were fixed in the study design and the number of treatment-cycles allowed in these studies varied but were limited to 6 cycles at most (see Appendix D). The "First line to progression" category included regimens where one or more treatments in the combination were allowed to be administered until progression and study regimens with fixed number of cycles and study regimens which allowed maintenance/continuation beyond "induction" were not considered comparable, even with the same drugs included. Accordingly, only studies reporting 'first line to progression' treatments were deemed relevant for inclusion in the NMA and were reported in Appendix D of the Company Submission."* The company did acknowledge that first line fixed cycle length (as opposed to until progression) treatments might be relevant to United Kingdom (UK) clinical practice, an example that is relevant to the decision problem being pembrolizumab with a 2-year stopping rule.[13] However, they claimed that *"…these treatment rules are a consequence of NICE guidance rather than the trial design themselves."*, so that *"…first line to progression studies would capture all relevant trials for the decision problem."* (p.35) In fact, the EAG notes that KEYNOTE-189 and KEYNOTE-189 Japan, two of the three trials of pembrolizumab combination with pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy included in the CS had a maximum treatment duration of 35 3-week cycles i.e., effectively a stopping rule at 2 years (see Section 3.3).[17, 18] However, treatment to progression applied up to this 2-year limit: *"…treatment was continued until radiographic progression, unacceptable toxic effects, investigator decision, or patient withdrawal of consent".*[19] The other included trial is KEYNOTE-021, which also had a stopping rule for pembrolizumab of 2 years, and applied the same criteria for discontinuation.[20] The same criteria also apply to clinical practice, as stated in the NICE recommendation for pembrolizumab with pemetrexed plus platinum chemotherapy in TA683.[21] Therefore, the company appear to have applied this rule of only including 'treat to progression' studies unnecessarily, and regardless of the rule the inclusion of KEYNOTE-021 and KEYNOTE-189 is appropriate to the NICE scope. The company did provide a list of all first line studies that they retrieved in the SLR and, given the decision problem, the only other studies that could be relevant would be those including pemetrexed and chemotherapy and the company argue that pemetrexed would only be used in clinical practice according to NG122 as "*maintenance*". However, TA181,[22] which is cited in NG122, recommends it for induction in combination with platinum chemotherapy and the EAG notes that several of the 12 studies listed by the company as first-line studies have a pemetrexed and chemotherapy arm, including the one on which TA181 is based.[23] This seems to imply that studies have been excluded erroneously. However, the EAG also notes that pemetrexed maintenance is recommended according to TA402 following induction with pemetrexed plus platinum chemotherapy. It also appears that the combination of induction and maintenance is effectively 'treat to progression' and how pemetrexed was administered in the three included trials of pemetrexed (KEYNOTE-189, KEYNOTE-189 Japan and KEYNOTE-021). Therefore, it seems probable that the company is

correct that applying the 'treat to progression' criterion, although perhaps for the wrong reason, has had no impact on inclusion of studies relevant to the scope.

- The company have also been asked to state if any comparator treatments are administered for a fixed number of cycles or for a fixed time period, if so then they were asked to include studies of those treatments. The company re-stated that, "*.. limiting the NMA to include only first line to progression studies will not have excluded any data relevant to the current appraisal*." The EAG does not think that the company have answered this question satisfactorily, although this probably does not have serious implications.
- Finally, the company were asked to verify that the criterion 'until progression' is equivalent to 'until progression or unacceptable toxicity'. The company stated that, "*Lilly can confirm that the criterion 'until progression' is equivalent to 'until progression or unacceptable toxicity*." The EAG thanks the company for this clarification.

In conclusion, the EAG was concerned that the narrowing of the evidence base to 'first line to progression studies' based on how selpercatinib treatment might be at odds with the NICE scope and company's own decision problem and therefore might not cover the required evidence base. However, it does appear that at least for the comparators in the decision problem this is consistent with NICE guidance and therefore National Health Service (NHS) clinical practice. In principle the effectiveness of pemetrexed and platinum chemotherapy 'treat until progression' could be estimated from a combination of trials at induction only and maintenance only, but it is unclear how this might be achieved technically. It also seems unnecessary given the availability of evidence for 'treat until progression' in the form of those three included studies KEYNOTE-189, KEYNOTE-189 Japan and KEYNOTE-021.

3.1.3 Critique of data extraction

All abstracts were reviewed independently by two systematic reviewers using the DistillerSR® tool, according to the eligibility criteria outlined in Table 3.2 above; any differences in opinion regarding eligibility were resolved through discussion with a third reviewer. The same process was applied to the subsequent review of full texts. The full texts were split according to the treatment line (first line, first-line to progression) and subsequently, each treatment line was considered independently for inclusion of studies and data extraction.

Sixty-six papers were initially chosen for inclusion in the SLR. As these included papers were collected for the ITC, also covering studies not involving selpercatinib, they have been described fully in Section 3.3. Only two included studies directly covered selpercatinib – LIBRETTO-001 and LIBRETTO-321- both of which were one arm trials.

EAG comment:

- As stated previously, the review protocol (Table 3.2) only appeared to specify RCTs and SLRs for inclusion. As there are no RCTs covering selpercatinib in the inclusion list, the SLR yielded no RCT data of direct relevance to the decision problem (selpercatinib versus the active comparators listed in Table 2.1).
- It is only the company's statement in the text of the appendices[8] that permits additional inclusion of, '*single-arm trials reporting data from patients with RET fusion-positive NSCLC and data from RCTs in the wider non-squamous NSCLC population',* that allows the studies from the one-arm LIBRETTO-001 and LIBRETTO-321 [24] trials to be included in the SLR. This amendment should have been reflected in the final protocol, for greater transparency. The company have been asked to comment on this, and stated that, "*At the time that the original SLR was conducted in July 2018,*

the comparator trials published in RET fusion-positive NSCLC were not of particular interest. For the update of the SLR conducted in July/August 2020, the protocol was amended in order to support selpercatinib HTA appraisals to include single arm trials for selpercatinib and pralsetinib. This reflected that both treatments were expected to have market access based on single arm clinical trials and that no RCT data were expected to be published. As such, this amendment was implemented in order that potentially relevant comparator information not be missed in the systematic review. Since the update to the SLR in July/August 2020, the single arm trials for specific RET inhibitors have been eligible for inclusion in the SLR." The EAG notes that the company response does not acknowledge the importance of presenting the most up-to-date protocol in the CS to maintain transparency.

- Despite being included in the SLR, the LIBRETTO-321[24] trial data was not presented in the clinical efficacy section of the CS[3], alongside the data from LIBRETTO-001. This issue is discussed in more detail in the next Section.

3.1.4 Quality assessment

Risk of bias assessments were carried out for all studies included in the SLR. For the first and second updates, the company stated that the risk of bias assessment was conducted in accordance with the Cochrane risk of bias tool described in the Cochrane Handbook. The company also stated that the risk of bias assessment for the third and fourth updates was conducted in line with the standards recommended by the NICE. Any single-arm trials identified vis SLR3 or SLR4 were assessed by the Critical Appraisal Skills Programme (CASP) cohort study checklist.

EAG comment: It is unclear why different RCT risk of bias criteria were used for different updates of the SLR: no rationale was provided by the company.

3.1.5 Evidence synthesis

No synthesis that was directly relevant to the decision problem (selpercatinib versus the active comparators listed in Table 2.1) was carried out. However, data from the SLR were synthesised in the NMA, which is dealt with in Sections 3.4.1 and 3.4.2.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

In the CS,[3] the company considered only one study - LIBRETTO-001 - which provided data on the efficacy and safety of selpercatinib. An overview of LIBRETTO-001 is included in Table 3.3.

EAG comment:

- Despite being included in the SLR, the LIBRETTO-321[24] trial data was not presented in the clinical efficacy section of the CS[3], alongside the data of LIBRETTO-001. The reasons for this are not provided by the company. The study appears eligible as it reports objective response rate (ORR) in RET fusion-positive NSCLC patients with advanced disease, where a subgroup (n=8) is treatment naïve. The company responded to the EAG request for clarification as follows: *"At the time that data extraction was ongoing for the clinical SLR, no results from the LIBRETTO-321 trial were available. As such, no data were extracted, but the first trial disclosure were captured in SLR5 from a congress abstract. A full manuscript was subsequently published after the SLR5 search date. The LIBRETTO-321 trial was conducted in China and recruited patients from China only. As noted in response to Question A17) above, there are known differences for the Asian race in NSCLC. As such, the generalisability a fully Asian cohort of patients to UK clinical practice is limited. In addition, at the time of the latest data cut off (March 2021), 47 patients diagnosed with RET-fusion*

positive NSCLC had been recruited, of which only 11 had their RET status confirmed. Of those with a confirmed RET status, only 8 patients were treatment naïve. Therefore, this change led to the exclusion of relatively immature data from only 8 patients, the results of which are anticipated to have limited applicability to the UK. Based on this, Lilly maintain that the amendment made was appropriate and did not lead to the exclusion of any relevant data". The EAG does not agree that LIBRETTO-321 should have been excluded as ethnicity was not an exclusion criterion on the review protocol (Table 3.2). Therefore LIBRETTO-321[24] trial results that are relevant to the decision problem (in the treatment-naïve (n=8) sub-group) have been added into Section 3.2 of this report.

- Randomised controlled trial data would be much more useful to this appraisal, and so it might have been prudent for the company to have delayed evidence submission until their ongoing RCT (LIBRETTO-431) yields data. Section B.2.10 of the CS[3] states: *"Results for LIBRETTO-431 are expected in December 2023. It is not anticipated for any data from this trial to become available during the course of this evaluation."* The company were asked to provide the earliest date by which an interim analysis from the randomised LIBRETTO-431 trial might be available, and the outcomes that will be presented. The company responded by stating that:[13] *"The interim analysis will be event driven and will be conducted when approximately* [redacted] *events in the primary outcome, PFS by BICR, have been observed in the ITT-pembrolizumab population. It is anticipated this criterion will be met in* [redacted]*, with results expected to be available from* [redacted]*."* The EAG have therefore identified this lack of RCT evidence in the RET fusion-positive population as a key issue (see Section 3.2.8).

3.2.1 Details of the included trials

3.2.1.1 LIBRETTO-001

LIBRETTO-001 is an ongoing multi-centre, open-label, single-arm, Phase I/II study in patients with advanced solid tumours, including RET fusion-positive NSCLC tumours. The patient population includes patients >12 years of age with a locally advanced or metastatic solid tumour, who fulfil one or more of the following criteria:

- progressed on standard therapy
- were intolerant to standard therapy
- were patients for whom no standard therapy exists
- weren't candidates for standard therapy
- would be unlikely to tolerate or derive significant clinical benefit from standard therapy
- declined standard therapy.

Patients are screened for eligibility based on the criteria presented in Table 3.3.

Table 3.3: Clinical effectiveness evidence

Study	LIBRETTO-001/LOXO-RET 17001 (NCT03157128)[25]
Study design	LIBRETTO-001 is a multicentre, open-label, single-arm, Phase I/II study that is ongoing. The trial is demarcated into two parts: Phase I (dose escalation) and Phase II (dose expansion).
Population	Patients ≥12 years old with locally advanced or metastatic solid tumours, including *RET* fusion-positive solid tumours (e.g. NSCLC, thyroid, pancreas or colorectal), *RET*-MTC and other tumours with RET activation, who progressed on or were intolerant to standard therapy, or no standard therapy exists, or in the opinion of the Investigator were not

Study	LIBRETTO-001/LOXO-RET 17001 (NCT03157128)[25]		
	candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or declined standard therapy and have an ECOG score of ≤2 or a LPS of ≥40%. As of 15 June 2021, N=796 patients had been enrolled onto the trial, of which N=356 were *RET* fusion-positive NSCLC patients, N=69 were treatment-naïve patients (SAS1 population). **Treatment-naïve *RET* fusion-positive NSCLC patients are the focus of this submission.**		
Intervention(s)	Selpercatinib, once or BID, depending on the dose level assignment. A recommended Phase II dose of 160 mg BID was selected during Phase I of the study.		
Comparator(s)	N/A – LIBRETTO-001 is a single arm trial		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use in the model	LIBRETTO-001 is the first trial demonstrating the efficacy, safety and tolerability of selpercatinib in patients with treatment-naïve *RET* fusion-positive NSCLC.		
Reported outcomes specified in the decision problem	Measures of disease severity and symptom control: • ORR • PFS • OS • HRQoL: • EORTC QLQ-C30 Safety outcomes: • AEs		
All other reported outcomes	DOR		

Based on Table 4, CS[3]
AEs = adverse events; BID = twice daily; CS = company submission; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questions C-30; HRQoL = health-related quality of life; LPS = Lansky Performance Score; MTC = medullary thyroid cancer; N/A = not applicable; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RET = rearranged during transfection

The study includes two phases: Phase I (dose escalation) in which patients were not selected based on RET alteration and Phase II (dose expansion), in which five cohorts of patients harbouring RET alterations were defined and in which the efficacy and safety of selpercatinib was assessed. The study is currently in Phase II.

Patients were subsequently enrolled into one of five Phase II cohorts to better characterise the safety and efficacy of selpercatinib in patients with specific abnormalities in RET. Classification into cohorts was based on tumour type, type of RET alteration and prior treatment (Table 3.4).

Table 3.4: LIBRETTO-001 patient cohorts: only Cohort 2 is relevant to this report

Patient cohort	Description
Cohort 1	*RET* fusion-positive solid tumour progressed on or intolerant to ≥1 prior standard first-line therapy, including *RET* fusion-positive NSCLC.
Cohort 2	*RET* fusion-positive solid tumour without prior standard first-line therapy, **including treatment-naïve *RET* fusion-positive NSCLC (SAS1 population).**
Cohort 3	*RET*-mutant MTC progressed on or intolerant to ≥1 prior standard first line cabozantinib and/or vandetanib.
Cohort 4	*RET*-mutant MTC without prior standard first line cabozantinib or vandetanib or other kinase inhibitors with anti-*RET* activity.
Cohort 5	Included patients from Cohorts 1 through 4 without measurable disease, MTC patients not meeting the requirements for Cohorts 3 or 4, MTC syndrome spectrum cancers or poorly differentiated thyroid cancers with other *RET* alteration/activation that could be allowed with prior Sponsor approval, cell-free DNA positive for a *RET* gene alteration not known to be present in a tumour sample.
Cohort 6	Patients otherwise eligible for Cohort 1 to 5 but who discontinued another selective *RET* inhibitor(s) due to intolerance are eligible with prior Sponsor approval.

Based on Table 5, CS[3]
CS = company submission; DNA = deoxyribonucleic acid; MTC = medullary thyroid cancer; NSCLC = non-small-cell lung cancer; RET = rearranged during transfection

Only a subset of patients in the LIBRETTO-001 trial are consistent with the population of relevance for this submission: 'treatment-naïve patients with advanced RET fusion-positive NSCLC who require systemic therapy', referred to as the Supplemental Analysis Set 1 (SAS1) or SAS1 population. These make up 69 of the 796 participants in the trial cohort and form cohort 2 in Table 3.4. In line with the decision problem for this submission, only results for the clinical effectiveness of selpercatinib in the 69 treatment-naïve patients with RET fusion-positive NSCLC (Cohort 2) will be included in this report.

Individual patients continued selpercatinib dosing at 160 mg BID in 28-day cycles until progressive disease (PD), unacceptable toxicity or other reasons for treatment discontinuation. The primary endpoint for the Phase II portion of the trial was ORR using RECIST v1.1. Secondary endpoints included DOR, PFS and OS, whilst the safety, tolerability and pharmacokinetic (PK) properties of selpercatinib were also considered.

EAG comment: The dose of selpercatinib is given as 160 mg BID. For other indications, the dose may be reduced for any participants weighing <50 kg. The company was asked if the dose of 160 mg BID was amended for any participants weighing <50 kg in the LIBRETTO-001 trial. If not, the company was asked to provide a rationale. If it was amended, the company was asked to clarify the number of participants affected. The company responded by stating that, "*In LIBRETTO-001, there were five patients with weight <50 kg at baseline, all of whom received 160 mg BID. Starting doses for patients in LIBRETTO-001 are presented in Table 4* [Table 3.5 below] *and were the doses used in the economic model. Weight was not a criterion for determining the starting dose, owing to LIBRETTO-001 being a Phase I/II study with a Phase I 'dose finding' phase which included dose escalation. As presented in Table 32 of the Company Submission, dose reductions were primarily due to the occurrence of adverse events. Drug dosage modifications and the reasoning for these modifications in the SAS1 population of the LIBRETTO-001 trial specifically are presented in Table 5* [Table 3.6 below]. *As shown, adverse events represented the majority of reasons for modifications. A total of* [redacted] *patients started on a lower*

dose of 80 mg BID, and this was due to the Phase I 'dose finding' nature of LIBRETTO-001. The company was also asked to confirm that the dosing in the economic model is precisely that in the LIBRETTO-001 trial. If not, the company was asked to describe any discrepancies and discuss the implications. The company stated that, "*Lilly can confirm that the dosing scheduled considered in the economic model was the same as in the LIBRETTO-001 trial."* The EAG appreciates the clarity of these responses and is satisfied with the information provided.

Table 3.5: Starting doses of patients in LIBRETTO-001

Dose (mg, twice daily), n (%)	SAS1 population (N=69)
160	[redacted]
120	[redacted]
80	[redacted]
40	[redacted]
All	[redacted]

Based on Table 4, Company response to clarification letter[13]
SAS1 = Supplementary Analysis Set 1

Table 3.6: Study drug dosage modifications in LIBRETTO-001

Study drug modification type and reason, n (%)	SAS1 population ([redacted])
Any dose reduction	[redacted]
Adverse event	[redacted]
Other reasons	[redacted]
Any dose withheld	[redacted]
Adverse event	[redacted]
Other reasons	[redacted]
Any dose increase	[redacted]
Intra-patient dose escalation	[redacted]
Dose re-escalation	[redacted]
Other reasons	[redacted]

Based on Table 5, Company response to clarification letter[13]
SAS1 = Supplementary Analysis Set 1

A summary of the methodology and trial design of LIBRETTO-001 is presented in Table 3.7 below.

Table 3.7: Summary of LIBRETTO-001 trial methodology

Trial name	**LIBRETTO-001**[25]
Location	A total of 85 investigational study sites across 16 countries worldwide have participated to date: United Kingdom, Canada, United States, Australia, Hong Kong, Japan, South Korea, Singapore, Taiwan, Switzerland, Germany, Denmark, Spain, France, Italy, Israel.
Trial design	A multicentre, open-label, single-arm, Phase I/II study in patients with advanced solid tumours, including RET-alterations.
Eligibility criteria for participants	**Inclusion criteria:** At least 18 years of age (for countries and sites where approved, patients as young as 12 years of age could be enrolled). Patients with a locally advanced or metastatic solid tumour who progressed on or were intolerant to standard therapy, or no standard therapy exists, or were not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy or declined standard therapy. For patients enrolled into the Phase II dose expansion portion of the study, evidence of a RET gene alteration in the tumour (i.e., not just blood), was required. ECOG performance status of 0, 1, or 2 (age ≥16 years) or LPS ≥40% (age <16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment. **Exclusion criteria:** Phase II Cohorts 1 through 4: an additional validated oncogenic driver that could cause resistance to selpercatinib treatment. Major surgery (excluding placement of vascular access) within 4 weeks prior to planned start of selpercatinib. Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment (with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least four weeks prior to the first dose of study treatment). Any unresolved toxicities from prior therapy greater than NCI CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy. Symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis or untreated spinal cord compression (unless neurological symptoms and CNS imagine are stable and steroid dose is stable for 14 days prior to first dose of selpercatinib and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery). Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of selpercatinib or prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) >470 msec on at least 2/3 consecutive ECGs and mean QTcF >470 msec on all three ECGs during screening.

	Active uncontrolled systemic bacterial, viral or fungal infection or clinically significant, active disease process, which in the opinion of the Investigator makes the risk: benefit unfavourable for the patient to participate in the trial. Screening for chronic conditions is not required. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug. Uncontrolled symptomatic hyperthyroidism or hypothyroidism. Uncontrolled symptomatic hypercalcaemia or hypocalcaemia. Pregnancy or lactation. Active second malignancy other than minor treatment of indolent cancers.
Method of study drug administration	Selpercatinib was administered in oral form. A RP2D of 160 mg BID was selected for Phase II based on results from Phase I of the study.
Permitted and disallowed concomitant medication	**Permitted:** Standard supportive medications used in accordance with institutional guidelines and Investigator discretion: Haematopoietic growth factors to treat neutropoenia, anaemia, or thrombocytopaenia in accordance with ASCO guidelines (but not for prophylaxis in Cycle 1). RBC and platelet transfusions. Anti-emetic, analgesic and antidiarrheal medications. Electrolyte repletion (e.g., calcium and magnesium) to correct low electrolyte levels. Glucocorticoids (approximately 10 mg per day prednisone or equivalent, unless there was a compelling clinical rationale for a higher dose articulated by the Investigator and approved by the Sponsor), including short courses to treat asthma, chronic obstructive pulmonary disease, etc. Thyroid replacement therapy for hypothyroidism. Bisphosphonates, denosumab and other medications for the treatment of osteoporosis, prevention of skeletal-related events from bone metastases and/or hypoparathyroidism. Hormonal therapy for patients with prostate cancer (e.g., gonadotropin-releasing hormone or luteinizing hormone-releasing hormone agonists) and breast cancer (e.g., aromatase inhibitors, selective estrogenic receptor modulators or degraders), that the patient was on for the previous 28 days. **Disallowed:** Prior treatment with a selective RET inhibitor(s). Concomitant systemic anti-cancer agents. Haematopoietic growth factors for prophylaxis in Cycle 1.

	Therapeutic monoclonal antibodies. Drugs with immunosuppressant properties. Medications known to be strong inhibitors or inducers of CYP3A4 (moderate inhibitors/inducers could be taken with caution. If patients received strong CYP3A4 inhibitors/inducers, then the Sponsor was consulted to determine whether to stop selpercatinib or remove the patient from the study). Herbal products, such as St John's wort, which could decrease the drug levels of selpercatinib. Investigational agents (other than selpercatinib). No new, alternative systemic anticancer therapy was allowed prior to documentation of PD. The concomitant use of PPIs was prohibited, and patients were to discontinue PPIs one or more weeks prior to the first dose of selpercatinib. Histamine type-2 blocking agents were required be administered only between 2 and 3 hours after the dose of selpercatinib Antacids e.g., aluminium hydroxide/magnesium hydroxide/simethicone or calcium carbonate, if necessary, were required to be administered 2 or more hours before and/or after selpercatinib.
Primary outcome	**Phase I:** Identification of the MTD and the RP2D of selpercatinib for further clinical investigation. **Phase II:** The primary endpoint was ORR based on RECIST v1.1 or RANO, as appropriate to the tumour type as assessed by IRC.
Secondary and exploratory outcomes	**Secondary endpoints:** Phase I: determination of the safety and tolerability of selpercatinib, characterisation of the PK properties and assessment of the anti-tumour activity of selpercatinib by determining ORR using RECIST v1.1 or RANO. Phase II: BOR, DOR, CBR, CNS ORR, CNS DOR, PFS, OS, AEs and changes from baseline in clinical safety laboratory values and vital signs, characterisation of PK properties. **Exploratory endpoints:** Determination of the relationship between PKs and drug effects (including efficacy and safety). Evaluation of serum tumour markers. Characterisation of RET gene fusions and mutations and concurrently activated oncogenic pathways by molecular assays, including NGS from tumour biopsies and cfDNA. Collection of PROs data to explore disease-related symptoms and HRQoL.
Pre-planned subgroups	The primary objective was analysed by several demographic variables for NSCLC patients enrolled in the trial: • Age (≥65 versus <65) • Sex (male versus female)

	• Race (white versus other) • ECOG (0 versus 1–2) • Metastatic disease (yes versus no) • CNS metastasis at baseline by investigator (yes versus no) The primary objective was also analysed by type of *RET* fusion partner and type of *RET* molecular assay used for NSCLC patients enrolled in the trial: Fusion partner: KIF5B CCDC6 NCOA4 KIAA1468 ARHGAP12 CCDC88C CLIP1 PRKAR1A RBPM and DOCK 1 TRIM24 Other Unknown Molecular assay: NGS on blood or plasma NGS on tumour PCR Other
Duration of study and follow-up	The study is ongoing. The first patient was treated on 9 May 2017. At the latest data cut-off of 15 June 2021, the median follow-up was 25.2 months for OS and 21.9 months for PFS for SAS1 (treatment-naïve) patients.[26] Patients continued selpercatinib dosing in 28-day cycles until PD, unacceptable toxicity or other reasons for treatment discontinuation. Four weeks (28 days + 7 days) after the last dose of study drug, all treated patients underwent a safety follow-up (SFU) assessment. All patients were also to undergo long term follow-up (LTFU) assessments every 3 months.
Based on Table 6, CS[3]	

ACTH = adrenocorticotropic hormone; AE = adverse event; ASCO = American Society for Clinical Oncology; BID = twice daily; BOR = best overall response; CBR = clinical benefit rate; CEA = carcinoembryonic antigen; cfDNA = circulating free DNA; CNS = central nervous system; CYP3A4 = cytochrome P450 3A4; DOR = duration of response; ECGs = electrocardiograms; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HRQoL = health-related quality of life; IRC = Independent Review Committee; LPS = Lansky Performance Score; LTFU = lost to follow-up; MTC = medullary thyroid cancer; MTD = maximum tolerated dose; NGS = next generation sequencing; NCI CTCAE = National Cancer Institute common terminology criteria for adverse events; ORR = objective response rate; OS = overall survival; PCR = polymerase chain reaction; PD = progressive disease; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PK = pharmacokinetic; PPI = proton pump inhibitors; PRO = patient reported outcome; QD = once daily; QTcF = QT interval corrected for heart rate using Fridericia's formula; RANO = response assessment in neuro-oncology criteria; RBC = red blood cell; RECIST = response evaluation criteria in solid tumours; *RET* = rearranged during transfection; RP2D = recommended Phase II dose; SAS1 = Supplemental Analysis Set 1; SFU = safety follow-up

3.2.1.2 LIBRETTO-321

LIBRETTO-321 is an open-label, one-arm, multicentre, phase II study (NCT04280081). It has been conducted in China at 15 sites. Patients with advanced RET-altered solid tumours received selpercatinib (160 mg orally BID) in a 28-day cycle. The primary endpoint was IRC-assessed ORR; RECIST v1.1. Secondary endpoints included duration of response, CNS response, and safety.

Inclusion criteria were age of 18 years or older, with a diagnosis of advanced RET fusion-positive NSCLC. The sub-group (n=8) of relevance to this report had RET fusion-positive NSCLC (with RET status confirmed by a central laboratory) and were treatment naive. Patients were also required to have an ECOG score of 0–2 with no sudden deterioration 2-weeks prior to the first dose of selpercatinib, a corrected QT interval of 470 msec or less, and adequate hematologic, hepatic, and renal function. Exclusion criteria were: no qualified RET alteration status, prior treatment with selective RET inhibitors (including investigational selective RET inhibitors), unresolved toxicities from prior therapy worse than grade 1 according to the common terminology criteria for adverse events (CTCAE), human immunodeficiency virus (HIV), history of active hepatitis B or C, symptomatic central nervous system (CNS) tumour, concurrent use of drugs prolonging QT interval corrected for heart rate (QTc), active secondary malignancy, pregnancy, and presence of additional oncogenic drivers that could cause resistance to selpercatinib.

A summary of the methodology and trial design of LIBRETTO-321 is presented in Table 3.8 below.

Table 3.8: Summary of LIBRETTO-321 trial methodology

Trial name	**LIBRETTO-321**[24, 27, 28]
Location	A total of 15 investigational study sites in China.
Trial design	A multicentre, open-label, single-arm, Phase II study in patients with advanced solid tumours, including RET-alterations.
Eligibility criteria for participants	**Inclusion criteria:** At least 18 years of age. Diagnosis of advanced RET fusion-positive NSCLC. The sub-group (n=8) of relevance to this report had RET fusion-positive NSCLC (with RET status confirmed by a central laboratory) and were treatment naïve. ECOG performance status of 0, 1, or 2 with no sudden deterioration two weeks prior to the first dose of study treatment. A corrected QT interval of 470 msec or less, and adequate hematologic, hepatic, and renal function. **Exclusion criteria:** No qualified RET alteration status. Prior treatment with selective RET inhibitors (including investigational selective RET inhibitors). Unresolved toxicities from prior therapy worse than grade 1 according to the CTCAE. HIV. History of active hepatitis B or C. Symptomatic CNS tumour. Concurrent use of drugs prolonging QTc Active secondary malignancy. Pregnancy. Presence of additional oncogenic drivers that could cause resistance to selpercatinib.
Method of study drug administration	Selpercatinib was administered orally (160 mg BID) in a 28-day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent.
Permitted and disallowed concomitant medication	**Permitted:** Not reported. **Disallowed:** Drugs prolonging QTc.
Primary outcome	The primary endpoint was ORR based on RECIST v1.1 .

Secondary and exploratory outcomes	**Secondary endpoints:** DOR. CNS response. Safety.
Pre-planned subgroups	None reported.
Duration of study and follow-up	9.7 months median follow up.

Based on Lu et al 2022[24]

BID = twice daily; CNS = central nervous system; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; CTCAE = common terminology criteria for adverse events; HIV = human immunodeficiency virus; QT = QT interval; QTc = QT interval corrected for heart rate; NSCLC =non-small-cell lung cancer; ORR = overall response rate; RECIST = response evaluation criteria in solid tumours; RET = rearranged during transfection

3.2.2 Statistical analysis of the included studies

3.2.2.1 LIBRETTO-001

There were five analysis sets in LIBRETTO-001 for patients with NSCLC (Table 3.9). In line with the decision problem, only clinical effectiveness data from treatment-naïve patients with measurable disease are considered in this submission. These patients comprised the SAS1 population.

Table 3.9: LIBRETTO-001 analysis set definitions

Analysis set	Analysis set description		Number of patients
Efficacy analysis (NSCLC)			
Primary Analysis Set (second line)	The first 105 *RET* fusion-positive NSCLC patients enrolled in Phase I and Phase II who met the following criteria: Evidence of a protocol-defined qualifying and definitive RET fusion, prospectively identified on the basis of a documented CLIA-certified (or equivalent ex-US) molecular pathology report. Patients with a RET fusion co-occurring with another putative oncogenic driver, as determined at the time of study enrolment by local testing, were included Measurable disease by RECIST v1.1 by IA[a]. Received 1 or more lines of prior platinum-based chemotherapy. Received 1 or more doses of selpercatinib.		105
Integrated Analysis Set (second line)	All *RET* fusion-positive NSCLC patients treated in LIBRETTO-001 by the data cut-off date who met PAS criteria 1 to 4. Included all PAS patients and those enrolled after the 105th patient but on or before the data cut-off.		247
Supplemental Analysis Sets	All other *RET* fusion-positive NSCLC patients (e.g., not part of the PAS/IAS) who were treated in LIBRETTO-001 as of the data cut-off date. SAS1 and SAS2: met PAS criteria 1, 2 and 4. SAS3: met PAS criteria 1 and 4. SAS assignment was non-overlapping; thus, SAS1 to 3 are mutually exclusive with each other.	**SAS1 (treatment-naïve; population of interest to this submission):** No prior systemic therapy.	**69**
		SAS2 (prior other systemic therapy): Received prior systemic therapy other than platinum-based chemotherapy.	[redacted]
		SAS3 (non-measurable disease): No measurable disease[b].	[redacted]
Safety analysis			
Overall Safety Analysis Set	Patients treated with selpercatinib as of a data cut-off of 15 June 2021.	**NSCLC Safety Analysis Set:** *RET* fusion-positive NSCLC	356
		RET-mutant MTC	[redacted]
		RET fusion-positive thyroid cancers	[redacted]

Analysis set	Analysis set description		Number of patients
Efficacy analysis (NSCLC)			
		RET fusion-positive other cancers	[redacted]
		Other cancers	[redacted]
		Total	**796**

Based on Table 7, CS[3]
[a] Patients without measurable disease who were enrolled in Phase I dose escalation were included in the PAS
[b] Patients without measurable disease who were enrolled into Phase I dose expansion Cohort 5 (per protocol version 4.0 or earlier) or Phase 2 Cohort 5 (per protocol version 5.0 and later)
CLIA = Clinical Laboratory Improvement Amendments; CS = company submission; IA = Investigator Assessment; IAS = Integrated Analysis Set; MTC = medullary thyroid cancer; NSCLC = non-small-cell lung cancer; PAS = Primary Analysis Set; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours, Version 1.1; RET = rearranged during transfection; SAS = Supplemental Analysis Set; SAS1 = Supplemental Analysis Set 1; SAS2 = Supplemental Analysis Set 2; SAS3 = Supplemental Analysis Set 3; SCE = Summary of Clinical Efficacy; US = United States

An interim analysis was conducted for 796 patients with advanced solid tumours who had enrolled in the LIBRETTO-001 trial as of a 15 June 2021 data cut-off.[29] Unless noted otherwise, the results presented and analysed in this submission are based on this data cut-off. The safety evaluable data set includes all 796 patients treated with selpercatinib as of the 15 June 2021 data cut-off.

Table 3.10: Statistical methods for the primary analysis of LIBRETTO-001

Trial name	LIBRETTO-001
Hypothesis objective	**Phase I:** The primary objective of Phase I was to determine the MTD and/or the RP2D of selpercatinib. **Phase II:** The primary objective of Phase II was to assess, for each Phase II expansion cohort, the anti-tumour activity of selpercatinib by determining ORR using RECIST v1.1 or RANO, as appropriate for the tumour type
Statistical analysis	Efficacy analyses were presented by Phase II cohort. Patients treated during the Phase I portion of the study who meet the Phase II eligibility criteria for one of the Phase II cohorts were included as part of the evaluable patients for that cohort for efficacy analyses. The analysis of response for the main body of this submission was determined by the IRC, while those assessed by the Investigator are presented in Appendix L.[8] For the primary endpoint, BOR for each patient (CR, PR, stable disease, PR, or unevaluable) occurring between the first dose of selpercatinib and the date of documented disease progression or the date of subsequent anticancer therapy or cancer-related surgery was determined based on the RECIST v1.1 criteria for primary solid tumours. All objective responses were confirmed by a second scan at least 28 days after the initial response. BOR was summarised descriptively to show the number and percentage of patients in each response category. The estimates of ORR were calculated based on the maximum likelihood estimator (i.e., the crude proportion of patients with best overall response of CR or PR) . Waterfall plots were used to depict graphically the maximum decrease from baseline in the sum of the diameters of target lesions. The estimate of the ORR was accompanied by 2-sided 95% exact binomial CIs. To assess the consistency of ORR across selected subgroups and special populations, prespecified supportive subgroup analyses were performed. These analyses were conducted in all the analysis sets including the SAS1 population.
Sample size, power calculation	**Phase I** The total number of patients to be enrolled in Phase I depended upon the observed safety profile, which determined the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD/RP2D for further study. If approximately 15 patients were enrolled in each planned dose cohort (Cohorts 1 to 8), a total of approximately 120 patients would be enrolled in Phase I. **Phase II** For Cohort 2, the population of relevance for this submission, (patients with *RET* fusion-positive solid tumours without prior standard first line therapy), a true ORR of ≥55% was hypothesised when selpercatinib was administered to such patients. A sample size of 59 patients was estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 35%.

Data management, patient withdrawals	Data censoring conditions for DOR, OS and PFS were as described below. If a patient met more than one of these conditions, then the scenario that occurred first was used for the analysis. **DOR and OS:** DOR and OS were right censored for patients who met one or more of the following conditions: • Subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression • Censored at the date of the last evaluable disease assessment prior to start of anticancer therapy or surgery • Died or experienced documented disease progression after missing two or more consecutively scheduled disease assessment visits • Censored at the date of the last evaluable disease assessment visit without documentation of disease progression before the first missed visit • Alive and without documented disease progression on or before the data cut-off date • Censored at the date of the last evaluable disease assessment **PFS:** • PFS was right censored for patients who met one or more of the following conditions: • No post-baseline disease assessments, unless death occurred prior to the first planned assessment (in which case death will be considered a PFS event) • Censored at the date of the first dose of selpercatinib • Subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression • Censored at the date of the last evaluable disease assessment prior to start of anticancer therapy or surgery • Died or documented disease progression after missing two or more consecutively scheduled disease assessment visits • Censored at the date of the last evaluable disease assessment visit without documentation of disease progression before the first missed visit • Alive and without documented disease progression on or before the data cut-off date • Censored at the date of the last evaluable disease assessment

Based on Table 8, CS[3]

BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; IRC = Independent Review Committee; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RP2D = recommended Phase II dose; RANO = response assessment in neuro-oncology criteria; RECIST = response evaluation criteria in solid tumours; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

A variety of outcomes were employed to explore the efficacy of selpercatinib in treatment-naïve patients with *RET* fusion-positive NSCLC. Definitions for these outcome measures are presented in Table 3.11.

Table 3.11: Definitions for outcome measures used in LIBRETTO-001

Outcome measure	Definition
Primary outcome	
Objective response rate	The ORR was defined as the proportion of patients with BOR of confirmed CR or confirmed PR based on RECIST v1.1. The BOR was defined as the best response designations for each patient recorded between the date of the first dose of selpercatinib and the data cut-off, or the date of documented disease progression per RECIST v1.1 or the date of subsequent therapy or cancer-related surgery. Definitions of response by RECIST v1.1 are as follows:[30] **Complete Response (CR)**: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. **Partial Response (PR)**: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. **Progressive Disease (PD)**: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Secondary outcomes	
Duration of response	The DOR was calculated for patients who achieved either a CR or PR. For such patients, DOR was defined as the number of months from the start date of CR or PR (whichever response was observed first) and the first date that recurrent or PD was objectively documented. If a patient died, irrespective of cause, without documentation of recurrent or PD beforehand, then the date of death was used to denote the response end date.
Progression-free survival	PFS was defined as the number of months elapsed between the date of the first dose of selpercatinib and the earliest date of documented PD, as per RECIST v1.1 or death (whatever the cause).
Overall survival	OS was defined as the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause).
EORTC QLQ-C30	The EORTC QLQ-C30 is a validated instrument that assesses HRQoL in adult cancer patients. It includes a total of 30 items and is composed of scales that evaluate physical (five items), emotional (four items), role (two items), cognitive (two items) and social (two items) functioning, as well as global health status (two items). Higher mean scores on these scales represent better functioning. There are also three symptom scales measuring nausea and vomiting (two items), fatigue (three items) and pain (two items), and six single items assessing financial impact and various physical symptoms. Higher mean scores on these scales represent better

Outcome measure	Definition
	functioning or greater symptomology. EORTC QLQ-C30 subscale scores range from 0 to 100. Descriptive analyses reported median/quartile, mean/SD and mean change/standard error from baseline for each subscale at each study visit. A minimal clinically meaningful difference was defined as at least a 10-point difference from the baseline assessment value for each patient, consistent with published work in oncology.[31] Patients with "improvement" were defined as those who demonstrated a ≥10-point improvement from their baseline score. Patients with "worsening" were defined as those who demonstrated a deterioration by ≥10-points from their baseline score. A sustained change (improvement or worsening) was defined as an improvement or worsening, respectively, (as defined above) without any further change in score ≥10 points.
Based on Table 9, CS[3] BOR = best overall response; CR = complete response; DOR = duration of response; EORTC QLQ = European Organisation for Research and Treatment of Cancer quality of life questionnaire; HRQoL = health-related quality of life; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease	

3.2.2.2 LIBRETTO-321

Only the analysis pertaining to the eight participants who were treatment naïve, and RET fusion-positive NSCLC is relevant to this report. The ORR was estimated based on the observed proportion of patients whose BOR was confirmed as CR or PR as determined by the IRC and the Investigator. The estimates of the ORR were accompanied by a two-sided 95% exact binomial confidence interval (CI) calculated using the Clopper-Pearson method.

3.2.3 Baseline characteristics

3.2.3.1 LIBRETTO-001

A summary of patient demographics and other baseline characteristics for the 69 patients in the SAS1 population with *RET* fusion-positive NSCLC enrolled in LIBRETTO-001 is provided below.

The median age of patients with in the SAS1 population was 63 (range: 23–92) years and a greater proportion of participants were female (62.3%; Table 3.12). The majority (69.6%) of patients were white, with a high proportion of patients identified as Asian (18.8%). Most participants (69.6%) reported never smoking. The younger age, as well as the higher proportion of females, Asian patients and non-smokers is reported by the company to be consistent with the patient profile of *RET* fusion-positive NSCLC reported in the literature and mirrors the real-world patient profile in England.

In the SAS1 population, the median time from diagnosis was [redacted] months ([redacted] Most patients (98.6%) had metastatic disease at enrolment, with 23.2% exhibiting CNS metastases at baseline. In addition, most patients were diagnosed with Stage IV or greater disease (91.3%). This was higher than England, where 46.8% of NSCLC patients were diagnosed at Stage IV in 2017. Next generation sequencing (NGS) on tumour samples [redacted] was the most common method of determining *RET* fusion status, which will mirror English clinical practice following the growing establishment of Genomic Hubs (Table 3.13).

In line with the population described in the decision problem, no patients in the SAS1 subgroup had received prior systemic therapy or treatment other than cancer surgery ([redacted]) or radiotherapy ([redacted] Table 3.14).

Table 3.12: Baseline demographic characteristics for treatment-naïve RET fusion-positive NSCLC patients (SAS1)

Characteristics	SAS1 (treatment-naïve), N=69
Age, years	
Median (range)	63.0 (23–92)
Age group, n (%)	
18–44 years	[redacted]
45–64 years	[redacted]
65–74 years	[redacted]
75 –84 years	[redacted]
≥85 years	[redacted]
Sex, n (%)	
Male	26 (37.7)
Female	43 (62.3)
Race, n (%)	
White	48 (69.6)
Black	4 (5.8)
Asian	13 (18.8)
Other/Missing	4 (5.8)
Ethnicity, n (%)	
Hispanic or Latino	[redacted]
Not Hispanic or Latino	[redacted]
Missing	[redacted]
Body weight, kg	
Median (range)	[redacted]
Baseline ECOG, n (%)	
0	[redacted]
1	[redacted]
2	[redacted]
Smoking history, n (%)	
Never smoked	48 (69.6)
Former smoker	19 (27.5)
Current smoker	2 (2.9)

Based on Table 10, CS[3]
CS = company submission; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small-cell lung cancer; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Table 3.13: Baseline disease characteristics for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)

Characteristics	SAS1 (treatment-naïve), N=69
Stage at diagnosis, n (%)	
I, IA, IB	[redacted]
II, IIA, IIB	[redacted]
IIIA, IIIB	[redacted]
IIIC	[redacted]
IV	[redacted]
IVA	[redacted]
IVB	[redacted]
IVC	[redacted]
Missing	[redacted]
Time from diagnosis, months	
Median (range)	[redacted]
History of metastatic disease, n (%)	
Yes	[redacted]
No	[redacted]
Time from diagnosis of metastatic disease, months	
Median	[redacted]
Range	[redacted]
At least one measurable lesion by investigator, n (%)	
Yes	[redacted]
No	[redacted]
Sum of diameters at baseline by investigator, mm	
Median (range)	[redacted]
CNS metastases at baseline by investigator, n (%)	
Yes	16 (23.2)
No	53 (76.8)
***RET* fusion partner, n (%)**	
KIF5B	48 (69.6)
CCDC6	10 (14.5)
NCOA4	1 (1.4)
Other	[redacted]
Unknown	[redacted]
Molecular assay type, n (%)	
NGS on tumour	[redacted]
PCR on tumour	[redacted]
NGS on plasma/blood	[redacted]
FISH on tumour	[redacted]

Characteristics	SAS1 (treatment-naïve), N=69
Nano string technology	[redacted]
Based on Table 11, CS[3] CNS = central nervous system; CS = company submission; FISH = fluorescent in situ hybridisation; NGS = next generation sequencing; NSCLC = non-small-cell lung cancer; PCR = polymerase chain reaction; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1	

Table 3.14: Prior cancer-related treatments for *RET* fusion-positive NSCLC

Characteristics	SAS1 (treatment-naïve), N=69
Prior systemic therapy, n (%)	
Yes	[redacted]
No	[redacted]
Prior radiotherapy, n (%)	
Yes	[redacted]
No	[redacted]
Prior cancer related surgery, n (%)	
Yes	[redacted]
No	[redacted]
Based on Table 12, CS[3] CS = company submission; NSCLC = non-small-cell lung cancer; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1	

The patient disposition of the SAS1 analysis set is presented in Table 3.15. Of the 69 patients included, [redacted] were still on treatment as of the 15 June 2021 data cut-off. For all patients, the most common reason for treatment discontinuation was [redacted].

Table 3.15: Patient disposition of *RET* fusion-positive NSCLC patients in the LIBRETTO-001 trial (15 June 2021 data cut-off)

Characteristics	SAS1 (treatment-naïve), N=69
Treated	**69**
Treatment ongoing, n (%)	**32 (46.4)**
Treatment discontinued, n (%)	[redacted]
Disease progression	[redacted]
Adverse event	[redacted]
Withdrawal of consent	[redacted]
Death	[redacted]
Other	[redacted]
Treatment continued post-progression, n (%)	[redacted]
Study status:	
Continuing study, n (%)	[redacted]
Discontinued study, n (%)	[redacted]
Reason for study discontinuation	
Withdrawal of consent	[redacted]
Death	[redacted]

Characteristics	SAS1 (treatment-naïve), N=69
Based on Table 13, CS[3] CS = company submission; NSCLC = non-small-cell lung cancer; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1	

EAG comment: Outcomes are presented and used in all analyses (ITC and CEA) for the SAS1 population of LIBRETTO, but it is unclear if the SAS1 population includes all eligible participants. The company was asked to confirm that the patients in the SAS1 are all the RET fusion-positive NSCLC patients that were included in LIBRETTO-001 and that there were no RET fusion-positive NSCLC patients treated in LIBRETTO-001 omitted from the SAS1. The company responded by stating that, *"Lilly can confirm that all treatment-naïve RET-fusion positive NSCLC patients enrolled into the LIBRETTO-001 trial were included in the SAS1 population"*.[13] The EAG appreciates this clarification.

3.2.3.2 LIBRETTO-321

Baseline characteristics for the eight participants who were treatment naïve are not presented in the paper. For the 26 who were RET fusion-positive NSCLC (but 18 of whom were *not* treatment naïve), the median age was 52, median weight was 60.6 kg, 88.5% had an ECOG of 1, and 19 had never smoked.

3.2.4 Subsequent therapy

No information on subsequent therapy was provided in the CS.[3]

EAG comment: The company was asked to provide the distribution of subsequent therapy in LIBRETTO-001, which they provided (see Table 3.16).[13] However, the EAG have found it difficult to reconcile these numbers to each other. The company were also asked to provide a comparison of these figures with NHS clinical practice and to discuss the implications of any discrepancies. In response, the company reproduced Table 61 from the CS as Table 8 in the clarification letter response.[3, 13] This is based on clinical expert opinion, which the EAG acknowledges might be necessary in the absence of experience of selpercatinib for this indication in the NHS. However, as the company point out, there is a large discrepancy between Table 61 and Table 3.16: Table 61 shows that clinical experts believe the following distribution (%) applies to clinical practice:

- Docetaxel 0
- Docetaxel plus nintedanib 0
- Nivolumab 0
- Pembrolizumab plus pemetrexed plus platinum chemotherapy 5
- Atezolizumab/pembrolizumab 5
- Pemetrexed plus platinum chemotherapy 70
- Best supportive care 20

However, notwithstanding the difficulty in reconciliation, in the LIBRETTO-001 it appears that very few patients received pemetrexed plus platinum chemotherapy and none received something that might be regarded as best supportive care. In contrast, it seems that about [redacted] received pembrolizumab in some combination. If there is a mismatch between the trial and NHS clinical practice, this could lead to two potential biases i.e., in effectiveness if a higher proportion of more effective immunotherapy combination treatments were administered in the trial, and in cost if the economic model assumed the lower proportion of those treatments. The potential mismatch in subsequent therapy distribution between LIBRETTO-001 and clinical practice therefore constitutes a key issue.

Table 3.16: Summary of subsequent therapies of patients in the LIBRETTO-001 trial

Type of anti-cancer therapy	SAS1 patients ([redacted]), n (%)	SAS1 patients who received subsequent therapy ([redacted]), %
Chemotherapy	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
TS-1	[redacted]	[redacted]
Avastin (bevacizumab)	[redacted]	[redacted]
Carboplatin/pembrolizumab	[redacted]	[redacted]
Carboplatin/pemetrexed/bevacizumab	[redacted]	[redacted]
Carboplatin, pemetrexed, pembrolizumab	[redacted]	[redacted]
Carboplatin, pemetrexed, and pembrolizumab	[redacted]	[redacted]
Carboplatin/pemetrexed/pembrolizumab	[redacted]	[redacted]
Maintenance pemetrexed and pembrolizumab	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Pemetrexed (Alimta)	[redacted]	[redacted]
Pemetrexed/pembrolizumab	[redacted]	[redacted]
Targeted therapies	[redacted]	[redacted]
Selpercatinib	[redacted]	[redacted]
BLU-667	[redacted]	[redacted]
ADC68, PDNA, tremelimumab and PF-06801591	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]
Pembrolizumab (Keytruda®)	[redacted]	[redacted]
Radiation to the right lung 5000CGY ended on 15 January 2020	[redacted]	[redacted]
Other	[redacted]	[redacted]
Avastin	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]

Based on Table 32, clarification letter response[13]
SAS1 = Supplemental Analysis Set 1

3.2.5 Risk of bias assessment

3.2.5.1 LIBRETTO-001

The LIBRETTO-001 trial was assessed for risk of bias and generalisability in line with NICE requirements. Overall, the results of the LIBRETTO-001 trial may be considered at low risk of bias, as summarised in Table 3.17.

Whilst LIBRETTO-001 was single arm in nature, the trial was reported by the company as having:

- a clearly focussed issue,
- accurately measured exposure and outcome to minimise bias, and
- results which were considered by the company to be precise, believable and generalisable to the UK population.

Table 3.17: Quality assessment of the LIBRETTO-001 trial

Study Question	Grade (Yes/No/Unclear)
1. Did the study address a clearly focussed issue?	Yes. The population was clearly defined, and the aim of the study was to assess the efficacy, safety, and pharmacokinetics of selpercatinib in patients with advanced solid tumours including *RET* fusion-positive solid tumours. The primary endpoint of Phase I was MTD and/or the RP2D of selpercatinib. The primary endpoint of Phase II was ORR and secondary endpoints include DOR, PFS and OS.
2. Was the cohort recruited in an acceptable way?	Clear inclusion and exclusion criteria are outlined in Drilon et al. 2020b[32]. However, it is an open-label, single-arm study, which could create selection bias.
3. Was the exposure accurately measured to minimise bias?	Yes. This was a prospective study with an appropriate study design with validated tools for outcome assessment and data collection. All patients were classified using the same criteria.
4. Was the outcome accurately measured to minimise bias?	Yes. Validated objective measurements were used. Tumour response was measured by RECIST v1.1 and assessed by an IRC. Adverse events were assessed using CTCAE. Neither the patients nor the outcome assessor were blinded as it was an open-label, single-arm study.
5A. Have the authors identified all important confounding factors? List the ones you think might be important, that the author missed.	No. Confounding factors were not listed; however, baseline characteristics are extensively reported.
5B. Have they taken account of the confounding factors in the design and/or analysis?	The study has no control arm; therefore, randomisation or stratification are not applicable.
6A. Was the follow up of subjects complete enough?	Yes. Out of the 69 subjects enrolled in the treatment-naïve cohort of LIBRETTO-001, a high proportion of patients (46.4%) were continuing treatment at the latest data cut-off.[29]
6B. Was the follow up of subjects long enough?	The follow-up of subjects was long enough to collect a sufficient number of PFS events and estimate the median, however the median OS was not estimable due to a low proportion of events.
7. What are the results of this study?	Selpercatinib was well-tolerated and had marked anti-tumour activity in treatment-naïve *RET* fusion-positive NSCLC patients, as illustrated by the ORR results.
8. How precise are the results?	The results were precise with RECIST assessment used on all scans to determine the ORR with an IRC. Response was confirmed by a repeat assessment no less than 28 days later.
9. Do you believe the results?	Yes. The primary endpoint for Phase II (ORR) aligns with published results from trials for other *RET* selective inhibitors.[33]

Study Question	Grade (Yes/No/Unclear)
10. Can the results be applied to the local population?	Yes. These results can be applied to treatment-naïve patients with *RET* fusion-positive NSCLC.
11. Do the results of this study fit with other available evidence?	Yes. The primary endpoint for Phase II (ORR) was similar to published results from trials for other *RET* selective inhibitors.[33] ORR was 70% in treatment-naïve NSCLC patients treated with pralsetinib in a Phase 1/2 trial compared to 84.1% in the LIBRETTO-001.
12. What are the implications of this study for practice?	The results from this small single-arm study show selpercatinib as a potential effective therapy for NSCLC patients with *RET*-altered tumours in both first- and subsequent lines of therapy.
Based on Table 14, CS[3] CS = company submission; CTCAE = common terminology criteria for adverse events; DOR = duration of response; IRC = Independent Review Committee; MTD = maximum-tolerated dose; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = response evaluation criteria in solid tumours; RET = rearranged during transfection; RP2D = recommended phase 2 dose	

EAG comment:

- The CASP appraisal checklist for cohort studies has been used. Questions 5A and 5B have not been answered satisfactorily. Evading the issue of confounding because of the lack of a comparator arm demonstrates a lack of understanding of confounding. Confounding – where outcomes are affected by variables other than the independent variable – does not only result from a mismatched comparator and will also occur in a single arm trial as a result of uncontrolled threats to internal validity, such as the placebo effect or history effects. These issues should have been mentioned in the comments. Therefore, the major flaw of this single arm trial – that it was not possible to extricate treatment effects from intervening effects because of the lack of a control arm – was not highlighted. The lack of appreciation of this is suggested by the company's comment for Question 7, where all of the improvement in outcomes in the single arm is uncritically attributed to a treatment effect, even though a complete absence of any contributary effect from intervening variables upon outcomes is extremely unlikely.
- Question 8 appears to have been misunderstood, with no comment on the precision of the estimates (for example, there should have been a comment on the spread of the 95% CIs relative to the null line).

3.2.5.2 LIBRETTO-321

The EAG used the CASP evaluation tool to assess the quality of the LIBRETTO-321 trial.[24]

Table 3.18: Quality assessment of the LIBRETTO-321 trial

Study Question	Grade (Yes/No/Unclear)
1. Did the study address a clearly focussed issue?	Yes.
2. Was the cohort recruited in an acceptable way?	Clear inclusion and exclusion criteria are outlined However, it is an open-label, single-arm study, which could create selection bias.
3. Was the exposure accurately measured to minimise bias?	Yes.

Study Question	Grade (Yes/No/Unclear)
4. Was the outcome accurately measured to minimise bias?	Yes. Validated objective measurements were used. Tumour response was measured by RECIST v1.1. Adverse events were assessed using CTCAE. Neither the patients nor the outcome assessor were blinded as it was an open-label, single-arm study.
5A. Have the authors identified all important confounding factors? List the ones you think might be important, that the author missed.	No.
5B. Have they taken account of the confounding factors in the design and/or analysis?	No.
6A. Was the follow up of subjects complete enough?	Yes.
6B. Was the follow up of subjects long enough?	The follow-up of 9.7 months was insufficient for valid measurement of outcomes. In the discussion the authors stated: "*at the time of analysis, many patients remained progression free, and responses were ongoing. Therefore, survival data were not mature, and median PFS and OS could not be estimated*"
7. What are the results of this study?	Selpercatinib had suggestions of marked anti-tumour activity in treatment-naïve *RET* fusion-positive NSCLC patients, as illustrated by the ORR results.
8. How precise are the results?	The results were precise with the 95% CI not crossing null for ORR.
9. Do you believe the results?	Yes. This aligns with results from LIBRETTO-001.
10. Can the results be applied to the local population?	Yes. These results can be applied to treatment-naïve patients with *RET* fusion-positive NSCLC.
11. Do the results of this study fit with other available evidence?	Yes. The primary endpoint for Phase II (ORR) was similar to published results from trials for other *RET* selective inhibitors.
12. What are the implications of this study for practice?	The results from this small single-arm study show selpercatinib as a potential effective therapy for NSCLC patients with *RET*-altered tumours in both first- and subsequent lines of therapy.

Based on Lu et al. 2022[24]
CI = confidence interval; CTCAE = common terminology criteria for adverse events; NSCLC = non-small-cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = response evaluation criteria in solid tumours; RET = rearranged during transfection

3.2.6 Efficacy results of the included studies

Outcomes have been ordered according to the NICE scope:

- OS
- PFS
- Response rate
- TTD
- Adverse effects of treatment
- HRQoL

EAG comment: The company additionally measured DOR, which has not been included in this report as it is not included in the NICE scope. This issue has been explored in detail in Section 2.4.

3.2.6.1 Overall survival

3.2.6.1.1 LIBRETTO-001

For assessment of OS, the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause) was recorded. Patients who were alive or lost to follow-up as of the data cut-off date were right-censored (see detailed censoring criteria listed in Table 3.10). The censoring date was determined from the date the patient was last known to be alive.

The median OS in the SAS1 trial population was [redacted] at the 15 June 2021 data cut-off, with the majority of patients (49; 71%) remaining alive at a median follow-up of 25.20 months. At 12 months, the OS rate was 92.7% (95% CI: 83.3–96.9) and at 24 months was 69.3% (95% CI: 55.2–79.7), providing preliminary evidence to support that selpercatinib will result in an extension to patients' lives (Table 3.19). The Kaplan-Meier (KM) plot for OS is presented in Figure 3.1.

Table 3.19: OS for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)

Criteria	SAS1 (treatment-naïve), N=69
Survival status n (%)[a]	
Dead	[redacted]
Alive	49 (71.0)
Duration of OS (months)	
Median[b]	[redacted]
95% CI	[redacted]
Minimum–maximum	[redacted]
Rate (%) of OS[b]	
12 months	92.7
95% CI	83.3–96.9
24 months	69.3
95% CI	55.2–79.7
Duration of follow-up (months)[c]	
Median	25.20
25th, 75th percentiles	[redacted]

Based on Table 18, CS[3]
[a] Status as of the patient's last disease assessment 15 June 2021
[b] Estimated based on Kaplan-Meier method
[c] 95% CI was calculated using Brookmeyer and Crowley method
[d] 95% CI was calculated using Greenwood's formula
CI = confidence interval; CS = company submission; NSCLC = non-small-cell lung cancer; NE = not estimable; OS = overall survival; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Figure 3.1: Kaplan-Meier plot of OS for treatment-naïve RET fusion-positive NSCLC (SAS1)

Based on Figure 8, CS[3]
Censored patients denoted by "+".
CS = company submission; NSCLC = non-small cell lung cancer; OS = overall survival; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

EAG comment: Evidence from LIBRETTO-001 is based on a 15 June 2021 data cut-off. Median OS was [redacted]. The company has been asked to provide evidence from a later cut-off and let the EAG know when the next data cut-off will be available. The company responded by stating that, "*At this current time, no data from a later data cut-off from the LIBRETTO-001 trial are available. The next data cut-off from the LIBRETTO-001 trial is anticipated to occur in* [redacted]*, with results expected to become available in* [redacted]". The EAG is satisfied with this response.

3.2.6.1.2 LIBRETTO-321

Survival data were not mature, and median OS could not be estimated.

3.2.6.2 Progression-free survival

3.2.6.2.1 LIBRETTO-001

Progression-free survival was derived for each patient as the number of months from the date of the first dose of the study drug until documented disease progression or death due to any cause. Patients were censored as per the criteria listed in Table 3.10.

As of the 15 June 2021 data cut-off, the majority (37; 53.6%) of patients were alive and without documented PD, with a median duration of PFS of 22 months (95% CI: 13.8–NE) months. Death or disease progression was reported in 29/69 (42%) of patients over a median follow-up of 21.9 months. Due to the majority of patients remaining progression-free at the cut-off date, the PFS data are considered immature (Table 3.20). The majority [redacted] of patients were progression-free for ≥12 months, as of the June 2021 data cut-off.

By KM estimates, the probability of patients being progression-free at 6- and 12- months was [redacted] and 70.6% (95% CI: 57.8–80.2), respectively, by Independent Review Committee (IRC) assessment. These results indicate that administration of selpercatinib can produce clinically meaningful responses for a high proportion of treatment-naïve patients, with over two thirds estimated to be event-free (death or disease progression) for at least a year after receiving their first dose. Progressed disease is associated with reduced patient HRQoL, and as such, selpercatinib is likely to bring positive benefits to treatment-naïve *RET* fusion-positive NSCLC patients by delaying disease progression and helping patients to maintain their QoL for longer periods of time. The KM plot of PFS is presented in Figure 3.2.

Table 3.20: PFS for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1; IRC assessment)

Criteria	SAS1 (treatment-naïve), N=69
Progression status n (%)[a]	
Disease progression	29 (42.0)
Died (no disease progression beforehand)	[redacted]
Censored	37 (53.6)
Reason censored (n, %)	
Alive without documented disease progression	[redacted]
Subsequent anti-cancer therapy or cancer-related surgery without document PD	[redacted]
Discontinued from study without documented PD	[redacted]
Discontinued treatment and lost to follow-up	[redacted]

Criteria	SAS1 (treatment-naïve), N=69
Duration of PFS (months)[b, c]	
Median	22.0
95% CI	[redacted]
Minimum–maximum	[redacted]
Rate (%) of PFS[b,d]	
≥6 months (95% CI)	[redacted]
≥12 months (95% CI)	70.6 (57.8–80.2)
≥24 months (95% CI)	41.6 (26.8–55.8)
≥36 months (95% CI)	[redacted]
Duration of PFS follow-up (months)[b]	
Median	22.0
25th, 75th percentiles	[redacted]
Observed PFS, n (%)	
<6 months	13 (18.8)
≥6 to 12 months	17 (24.6)
≥12 to 18 months	13 (18.8)
≥18 to 24 months	13 (18.8)
≥24 months	13 (18.8)

Based on Table 17, CS[3]
[a] Status as of the patient's last disease assessment 15 June 2021
[b] Estimated based on KM method
[c] 95% CI was calculated using Brookmeyer and Crowley method
[d] 95% CI was calculated using Greenwood's formula
CI = confidence interval; IRC = Independent Review Committee; KM = Kaplan-Meier; NSCLC = non-small-cell lung cancer; PD = progressive disease; PFS = progression-free survival; NE = not estimable; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Figure 3.2: Kaplan-Meier plot of PFS based on IRC assessment for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)

Based on Figure 7, CS[3]
Censored patients denoted by "+".
CS = company submission; IRC = Independent Review Committee; NSCLC = non-small-cell lung cancer; PFS = progression-free survival; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

3.2.6.2.2 LIBRETTO-321

Survival data were not mature, and median PFS could not be estimated.

3.2.6.3 Response Rate

3.2.6.3.1 LIBRETTO-001

The ORR was defined as the proportion of patients with a BOR of confirmed CR or PR based on RECIST v1.1 (see Table 3.11). In the SAS1 trial population, the ORR was 84.1% (58/69, 95% CI: 73.3–91.8) as per IRC assessment (Table 3.21). Based on BOR, 9% of patients were assessed to have stable disease, whilst the majority were assessed to have a partial response (78.3%). Only three patients (4%) were assessed to have PD as BOR.

The individual patients' responses to selpercatinib treatment in terms of percentage decrease in tumour size from baseline, as per RECIST v1.1, are illustrated in Figure 3.3, demonstrating that at the data cut-off, tumour diameter had decreased in all of the 69 patients, decreasing by more than 30% (i.e., at least a partial response was achieved) in all but [redacted] patients. The company concludes that these results indicate that selpercatinib treatment results in high response rates in treatment-naïve *RET* fusion-positive NSCLC patients, delaying disease progression and decreasing tumour size.

Table 3.21: BOR and ORR for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1; IRC assessment)

Criteria	SAS1 (treatment-naïve), N=69
Best overall response, n (%)	
Complete response	4 (5.8)
Partial response	54 (78.3)
Stable disease	6 (8.7)
Progressive disease	3 (4.3)
Not evaluable	2 (2.9)
Objective response rate (CR plus PR)	
n (%)	58 (84.1)
95% CI	(73.3–91.8)

Based on Table 15, CS[3]
BOR = best overall response; CI = confidence interval; CS = company submission; CR = complete response; IRC = Independent Review Committee; NSCLC = non-small-cell lung cancer; PR = partial response; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Figure 3.3: Waterfall plot of best change in tumour burden based on IRC assessment for treatment-naïve *RET* fusion-positive NSCLC patients (SAS1)

Based on Figure 5, CS[3]

Footnotes: Dotted lines indicate thresholds for PR and PD. A decrease in tumour size of ≥30% was considered a PR, whilst an increase in tumour size of ≥20% was considered

PD.

CS = company submission; IRC = Independent Review Committee; NSCLC = non-small-cell lung cancer; PD = progressive disease; PR = partial response; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

3.2.6.3.2 LIBRETTO-321

The BOR and ORR were evaluated by LIBRETTO-321 [24] (Table 3.22). The ORR was 87.5% (95% CI: 47.3 to 99.7).

Table 3.22: BOR and ORR for treatment-naïve *RET* fusion-positive NSCLC patients

Criteria	N=8
Best overall response, n (%)	
Complete response	1(12.5)
Partial response	6(75.0)
Stable disease	1(12.5)
Progressive disease	0
Not evaluable	0
Objective response rate (CR plus PR)	
n (%)	7 (87.5)
95% CI	(47.3–99.7)

Based on Lu et al 2022.[24]
BOR = best overall response; CI = confidence intervals; CR = complete response; NSCLC = non-small-cell lung cancer; ORR = objective response rate; PR = partial response; RET = rearranged during transfection

3.2.6.4 Time to treatment discontinuation

No data presented by company.

3.2.6.5 Health-related Quality of Life

3.2.6.5.1 LIBRETTO-001

The EORTC QLQ-C30 was used as the treatment-specific quality of life (QoL) measure.

As of the 15 June 2021 data cut-off, [redacted] patients in the SAS1 trial population had completed a baseline assessment as part of a "QLQ-C30 Analysis Set" and at least one following assessment. The EORTC QLQ-C30 questionnaires were administered at baseline and completed approximately every 8 weeks during the first year, at visit 13 and then every 12 weeks until the end of treatment (EoT) visit, and then at the follow-up visit after treatment discontinuation (see Table 3.11 for further details of EORTC QLQ-C30 methodology).

During treatment, [redacted] of patients experienced meaningful improvements (of at least 10 points) in the global health status/QoL subscale. With regards to physical, emotional, role and cognitive function, [redacted], [redacted] and [redacted] of patients, respectively, reported meaningful improvements during treatment with selpercatinib. Improvements were also seen in the EORTC QLQ-C30 subscales testing symptomology and financial impact of the disease. Of the [redacted] patients who completed the assessments, [redacted] reported an improvement in nausea and vomiting, [redacted] in fatigue, [redacted] in pain, [redacted] in dyspnoea, [redacted] in insomnia, [redacted] in appetite loss, [redacted] in constipation, [redacted] in diarrhoea and [redacted] in financial difficulties.

Across the majority of the QLQ-C30 subscales, a numerically higher proportion of NSCLC patients reported improved scores versus worsening QLQ-C30 subscale scores (Table 3.23). Overall, at the data cut-off the majority of treatment-naïve advanced *RET* fusion-positive NSCLC patients had improved QoL as determined by QLQ-C30 subscales during treatment with selpercatinib.

Table 3.23: EORTC QLQ-C30: Proportion of patients with *RET* fusion-positive NSCLC who improved or worsened from baseline at scheduled follow-up visits

QLQ-C30 Subscale, n (%)	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11	Cycle 13	Cycle 16	Cycle 19	Cycle 22	Cycle 25	Cycle 28	EoT
Global health status/QoL												
N	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Physical functioning												
N	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Emotional functioning												
N	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Role functioning												
N	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Cognitive functioning												
N	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Social functioning												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											

QLQ-C30 Subscale, n (%)	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11	Cycle 13	Cycle 16	Cycle 19	Cycle 22	Cycle 25	Cycle 28	EoT
Nausea and vomiting												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Fatigue												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Pain												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Dyspnea												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Insomnia												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Appetite loss												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Constipation												
n	[redacted]											

QLQ-C30 Subscale, n (%)	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Cycle 11	Cycle 13	Cycle 16	Cycle 19	Cycle 22	Cycle 25	Cycle 28	EoT
Improved	[redacted]											
Worsened	[redacted]											
Diarrhoea												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											
Financial difficulties												
n	[redacted]											
Improved	[redacted]											
Worsened	[redacted]											

Based on Table 19, CS[3]
Footnotes: Patients who were "improved" were defined as those who demonstrated a ≥10-point change from their baseline score. Patients who "worsened" were defined as those who demonstrated a decrease by ≥10-points from their baseline score
CS = company submission; EORTC QLQ = European Platform of Cancer Research Quality of Life Questionnaire; EoT = end of treatment; NSCLC = non-small-cell lung cancer; QoL = quality of life; RET = rearranged during transfection

3.2.6.5.2 LIBRETTO-321

Health-related quality of life data were not presented.

3.2.7.5 Sub-grouping

3.2.7.5.1 LIBRETTO-001

As described in Table 3.7, to assess the consistency of ORR across selected subgroups and special populations, prespecified supportive subgroup analysis based on demographic and baseline characterises was performed on the SAS1 trial population. The ORR remained consistent across the prespecified subgroups, demonstrating the efficacy of selpercatinib to be robust to variations in demographics and baseline characteristics (Figure 3.4 and Figure 3.5).

In addition, owing to the high prevalence of brain metastases in *RET* fusion-positive NSCLC patients the efficacy of selpercatinib in the subset of patients with brain metastases was investigated. A total of 16 (23.2%) of the 69 treatment-naïve patients had Investigator assessed brain metastases at baseline. Five patients had measurable CNS disease by IRC and 11 patients had non-measurable CNS disease by IRC. Figure 3.5 shows the effect on ORR.

The CS also reported that patients with measurable CNS lesions had a CNS ORR of [redacted]) demonstrating efficacy of selpercatinib against CNS metastases (Table 3.24).

Figure 3.4: Forest plots for the subgroup analysis on the ORR based on demographic characteristics (SAS1)

Based on Figure 9, CS[3]

Footnote: Two-sided 95% exact binomial CI is calculated using the Clopper-Pearson method. Dashed reference line is set at 30%. Solid reference line is set at 84.1% (overall ORR). Higher ORR values correspond to more favourable response outcomes to selpercatinib in the specified subgroup.

CI = confidence interval; CS =company submission; ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Figure 3.5: Forest plots for the subgroup analysis on the ORR based on baseline disease characteristics (SAS1)

Based on Figure 10, CS[3]

Footnote: Two-sided 95% exact binomial CI is calculated using the Clopper-Pearson method. Dashed reference line is set at 30%. Solid reference line is set at 84.1% (overall ORR). Higher ORR values correspond to more favourable response outcomes to selpercatinib in the specified subgroup.
CI = confidence interval; CNS = central nervous system; CS = company submission; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridisation; NGS = next generation sequencing; ORR = objective response rate; PCR = polymerase chain reaction; PD-1 = programmed cell death 1 receptor; PD-L1 = programmed cell death receptor ligand 1; RET = rearranged during transfection; SAS1 = Supplemental Analysis Set 1

Table 3.24: CNS ORR and DOR by IRC assessment - RET fusion-positive treatment-naïve patients with measurable CNS lesions

	NSCLC with prior RT			No prior brain RT (N=3)	All NSCLC (SAS1) (N=5)
	Brain RT ≤2 months prior to first dose (N=2)	Brain RT >2 months prior to first dose (N=0)	All NSCLC with prior RT (N=2)		
CNS ORR[a] (CR plus PR)					
Number of Patients with CR plus PR (n, %)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
95% CI[b]	[redacted]	N/A	[redacted]	[redacted]	[redacted]
CNS CBR					
Number of patients with CR plus PR plus SD[c] (n, %)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
95% CI[b]	[redacted]	N/A	[redacted]	[redacted]	[redacted]
CNS DOR (months)[d]					
Number of patients censored, n (%)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
Median (95% CI)	[redacted]	N/A	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	N/A	[redacted]	[redacted]	[redacted]

Based on Table 20, CS[3]

[a] CNS ORR is defined as the proportion of patients with best overall response of CR or PR. Response was confirmed by a repeat assessment no less than 28 days

[b] 95% CI was calculated using Clopper-Pearson method

[c] Indicates SD lasting ≥ 16 weeks following initiation of selpercatinib until the criteria for disease progression was first met

[d] Estimate based on KM method

[+] Censored observation

CBR = clinical benefit rate; CI =confidence interval; CNS = central nervous system; CR = complete response; CS = company submission; DOR = duration of response; IRC = Independent Review Committee; KM = Kaplan_Meier; N = number of patients; n = number of patients in specific category; N/A = not applicable; NSCLC = non-small-cell lung cancer; ORR = objective response rate; PR = partial response; RET = rearranged during transfection; RT = radiation therapy; SD = standard deviation

EAG comment:

- Subgrouping was planned for the existence of brain metastases. The company was asked to justify the choice of this sub-grouping variable in terms of how the existence of brain metastases are expected to influence the efficacy of selpercatinib. The company responded by stating that, "*A subgroup analysis to assess overall responses rates based on the RECIST 1.1 criteria, assessed by IRC, in patients with Investigator assessed brain metastases was performed in LIBRETTO-001. Differential efficacy of selpercatinib in this subgroup of patients was not anticipated as compared with RET-fusion positive patients without brain metastases, however this subgroup analysis was pre-specified owing to the high prevalence of brain metastases in patients with RET rearrangements, with an estimated lifetime prevalence of 46% in Stage IV disease, and the detrimental impact of brain metastases on survival. A real-world evidence study estimated a significantly shorter life expectancy for NSCLC patients with brain metastases (25.3 weeks) compared with patients with metastases in the contralateral lung (50.5 weeks), bone (49.4 weeks), adrenal glands (48.7 weeks) and liver (44.9 weeks) (p<0.01 for all comparisons). Available clinical data for selpercatinib evidences its high efficacy in RET fusion positive patients with brain metastases: the Summary of Product Characteristics (SmPC) for selpercatinib states that in 23 RET fusion-positive NSCLC patients with measurable CNS lesions in the LIBRETTO-001 trial, the overall response rate (ORR) in the evaluable patients was 87%.19 These data are supported by the subgroup analysis performed in the SAS1 (treatment-naïve NSCLC) trial population of the LIBRETTO-001 trial which found that patients with measurable CNS lesions had a CNS ORR of* [redacted]." This response appears to imply that the aim of the sub-group analysis was to demonstrate that despite the worse prognosis for people with brain metastases, the efficacy of selpercatinib is independent of the existence of brain metastases. The point estimates in Figure 3.5 do not appear to support the notion that the efficacy of selpercatinib is independent of the existence of brain metastases, as a clear difference in ORR point estimates exists between the sub-groups. Although there is probably some uncertainty, the analysis was almost certainly underpowered to detect a significant difference in effect between the sub-groups, and so the prudent response to this would be to state that a type II error may be responsible for the 'lack of significance', and that a true sub-group difference *may* exist (even if undetected as a statistically significant effect). The company's conclusion that selpercatinib efficacy is unaffected by the existence of brain metastases is therefore not supported by the evidence. The EAG therefore deem brain metastases to be a potential treatment effect modifier (see Section 3.4.1.5 regarding covariates in the ITC).
- Subgrouping was also planned for 'race'. In the baseline characteristics table in the CS[3] (Table 10) four categories are provided: White, Black, Asian and Other. However in the subgroup analyses in Figure 9 of the CS[3] only three categories are used: White, Asian and Other. Notwithstanding the expected small numbers (that are observed in other subgroup analyses), the company was asked to redo the sub-group analysis for 'race' using all four categories. The company stated that, "*In the SAS1 population of patients in the LIBRETTO-001 trial, there were only 4 patients recorded as 'Black or African American' patients, 4 recorded as 'Other' and 13 recorded as 'Asian'. Therefore, performing subgroup analyses based on these patient numbers would introduce substantial imprecision and potentially bias given that in a subgroup of 4 patients, the estimates might be very far from the subgroup population average. This would occur even if Lilly were to combine the 'Black or African American' subgroup into the 'Other' subgroup; the resulting population size of 8 would still be too small to provide robust and reliable subgroup results. Given that Lilly do not want to exclude these patients from the analysis or combine them with the 'Asian' subgroup, given the known differences for Asian ethnicity, subgroup analyses will not be carried out using all four categories*". The EAG is disappointed that sub-grouping could not be carried out as requested. The

problems arising from the small groups are fully understood by the EAG, and these would have been fully taken into account when interpreting the sub-grouped data. The EAG regards the incomplete sub-group analysis for 'race' to prohibit the assumption that race is not an outcome modifier. However, the EAG notes that the results that are available from the incomplete sub-group analysis suggest that race is not a treatment effect modifier and that results from a full subgroup analysis may not improve clarity on this matter given they would be subject to significant uncertainty owing to the low patient numbers available.

Table 3.25. Ethnicity of patients with *RET* fusion-positive NSCLC lung cancer in LIBRETTO-001

Race, n (%)	SAS1 population (N=69)
White	[redacted]
Black or African American	[redacted]
American Indian or Alaska Native	[redacted]
American Indian or Other Pacific Islander	[redacted]
Asian	[redacted]
Other	[redacted]
Missing	[redacted]

Based on Table 6, Company response to clarification letter.[13]
SAS1 = Supplemental Analysis Set 1

- Any discrepancies between the characteristics of the trial sample and the UK target population may have an impact on the applicability of the trial, provided that discrepant variables are potential outcome modifiers. Given that age, sex, race, ECOG, metastatic disease and CNS metastasis have been identified by the company as potential outcome modifiers (by virtue of being used in pre-planned sub-groups) the company was asked to provide data for the UK target population for each of these variables (using the categories employed in the baseline characteristics tables (CS,[3] Tables 10 and 11)). The company responded by stating that, "*RET fusion-positive NSCLC is a rare condition, with an upper estimate of 2% of all lung cancer cases exhibiting RET-fusion. Therefore, there is a lack of data specific to this population of patients in the UK. Despite this, a Lilly-commissioned survey provided some real-world insights on the characteristics of NSCLC patients from 9 countries, including the UK. Characteristics of the 74 UK patients with treatment-naïve RET fusion-positive advanced NSCLC included in the survey are presented in* [Adelphi DSP survey, Table 3.26]. *Due to the rarity of the disease, data for patients with metastatic disease and CNS metastasis specific to the UK are not available. The characteristics of patients in the survey are broadly aligned with the baseline characteristics of patients in the SAS1 population of the LIBRETTO-001 trial: median age (64.7 versus* [redacted] *years, respectively) and the proportion of patients who were not Hispanic or Latino (99% versus* [redacted]*%, respectively) were similar. In addition, the majority of patients (70%) in the survey were found to have an ECOG score of 1, which aligned with the patient characteristics reported in LIBRETTO-001 (58.0%). However, the proportion of males with treatment-naïve advanced NSCLC in the real-world data was higher than reported in LIBRETTO-001 (54% versus 37.7%)*" The EAG appreciates the data provided by the company on the 74 UK participants with treatment-naïve RET fusion-positive advanced NSCLC in the Adelphi DSP survey. The data showed similarities between the UK sample and the SAS1 trial dataset in age, with some differences in sex, ECOG score and molecular assay type. Although the data on ethnicity were similar between the UK sample and the SAS1 trial dataset, these data did not

differentiate between important ethnic groups in the UK. No data were provided for UK patients on history of metastatic disease.

- Meanwhile, the sub-group analyses demonstrated that any metastatic disease, CNS metastases, and age may be effect modifiers, and the incomplete sub-group analysis of 'race' means that 'race' cannot be excluded as an effect modifier. Whilst it is true that none of the results of the subgroup analysis were found to be statistically significant, a lack of statistical significance is not particularly informative in analyses that were not sufficiently powered, and the EAG believes that the point estimate differences are of sufficient magnitude to imply the possibility of type II errors.
- Therefore, the possibility that any metastatic disease, CNS metastases and race may differ between trial and target population (in the absence of adequate information) and the evidence that CNS metastases and race are possible effect modifiers make it possible that the effects in the trial may not be applicable to those that might be observed in the target population. This has therefore been designated as a key issue, although this is probably not resolvable due to lack of information.

Table 3.26. Characteristics of patients with treatment-naive advanced NSCLC from Adelphi DSP real-world evidence insights and LIBRETTO-001 trial

Characteristics	NSCLC DSP Wave IV, N=74	SAS1 (LIBRETTO-001). N=69
Age, years		
Median	64.7	63.0
Sex, n (%)		
Male	39 (53)	26 (37.7)
Female	35 (47)	43 (62.3)
Race/ethnicity, n (%)		
Hispanic/Latino	1 (1)	[redacted]
Not Hispanic or Latino	73 (99)	[redacted]
Missing	0 (0)	[redacted]
ECOG score at advanced diagnosis, n (%)		
0	11 (15)	25 (36.2)
1	52 (70)	40 (58.0)
2	7 (9)	4 (5.8)
3	1 (1)	0 (0.0)
4	3 (4)	0 (0.0)
Current disease stage, n (%)		
IV or greater	74 (100)	[redacted]
Investigator reported history of metastatic disease, n (%)		
Yes	NR	[redacted]
No	NR	[redacted]
Molecular assay type, n (%)		
NGS with tumour tissue	10 (37)	[redacted]
PCR on tumour	6 (22)	[redacted]
FISH on tumour	15 (56)	[redacted]
NGS on plasma/blood	0 (0)	[redacted]

Nano string technology	0 (0)	[redacted]

Based on Table 7, company response to clarification.[13]
ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in-situ hybridisation; NGS = next generation sequencing; NSCLC = non-small-cell lung cancer; NR = not reported; PCR = polymerase chain reaction; SAS1 = Supplemental Analysis Set 1

- It is pointed out in the CS[3] that 91.3% of those in the SAS1 dataset had stage IV or greater disease, and that this differs from the proportion of patients in England, where the figure is 46.8%. Given this large discrepancy, a sub-group analysis for cancer stage would appear to be appropriate, even though numbers in the group below stage IV will be small. The company was asked to carry out a sub-group analysis for cancer stage. The company responded by stating that, "*Disease stage reported in the LIBRETTO-001 trial is based on initial diagnosis and it is unclear whether data from the English National Cancer Registration database are based on initial diagnosis or based on re-assessment. Therefore, these data may not be generalisable. In addition, the eligibility criteria for the LIBRETTO-001 trial stipulated that patients must have locally advanced or metastatic disease. As patients with advanced disease typically have Stage IIIB disease or higher, the proportion of patients with Stage IV disease in the LIBRETTO-001 trial will inherently be higher and therefore will not be generalise to the proportion of patients with Stage IV disease out of the NSCLC population in England (which includes both early and advanced disease patients). Therefore, due to this analysis group not being generalisable to England NSCLC statistics, a subgroup analysis is not appropriate*." In view of the above response, the EAG agrees that a sub-group analysis for stage might be unnecessary. The NICE scope, and also the company's decision problem, specify 'advanced disease', which might explain the lack of agreement with the English National Cancer Registration figures that are based on all stages of disease.

3.2.7.5.2 LIBRETTO-321

No sub-grouping was undertaken.

3.2.8 Adverse events

3.2.8.1 LIBRETTO-001

The two safety analysis sets utilised in LIBRETTO-001 that were pertinent to this submission are as follows:

1. The Overall Safety Analysis Set (OSAS, N=796) includes all patients, regardless of tumour type or treatment history, who were enrolled in LIBRETTO-001 and received one or more doses of selpercatinib as of the 15 June 2021 data cut-off date.
2. The NSCLC Safety Analysis Set (SAS) (N=356) includes all patients with documented RET fusion-positive NSCLC who were enrolled in LIBRETTO-001 and received one or more doses of selpercatinib as of the 15 June 2021 data cut-off date.

Both safety analysis sets included all 69 treatment-naïve patients with documented RET fusion-positive NSCLC who are the focus of this submission.

3.2.8.1.1 Treatment duration and dosage

Informed by the Phase I dose escalation stage of LIBRETTO-001, the RP2D was 160 mg BID. The range of starting doses and average time on treatment were available for the SAS1 trial population (Table 3.27). Nearly all (66/69 (95.7%)) patients in the SAS1 trial population received the

proposed starting dose of 160 mg BID. The mean time on treatment was 18.27 months with a range between 0.4 and 41.2 months. The relative median dose intensity was similar in the Overall Safety Population (94.46%) and in the RET fusion-positive NSCLC Safety Population (92.71%) (Table 3.28).

Dose reductions were required in [redacted] patients in the OSAS and [redacted] patients in the RET fusion-positive NSCLC SAS, with the most common reason being adverse events (AEs; [redacted] [41%] and [redacted], respectively) (Table 3.29). Dose interruptions occurred in [redacted] of the OSAS and [redacted] of the NSCLC SAS, with the most common reason being AEs ([redacted] and [redacted], respectively). There were [redacted] and [redacted] dose increases in the OSAS and NSCLC SAS, respectively.

Table 3.27: Selpercatinib dosing (SAS1)

	SAS1 (treatment- naïve), (N=69)
Starting dose, n (%)	
80 mg BID	[redacted]
160 mg BID (RP2D)	[redacted]
240 mg BID	[redacted]
Time on treatment, months	
Mean (SD)	[redacted]
Median (range)	[redacted]

Based on Table 30, CS[3]
BID = twice daily; CS = company submission; RP2D = recommended Phase II dose; SAS1 = Supplemental Analysis Set 1; SD = standard deviation

Table 3.28: Selpercatinib relative dose intensity (Safety Analysis Sets)

	SAS (*RET* fusion-positive NSCLC; N=356)	**OSAS (overall population; N=[redacted])**
Relative dose intensity, n (%)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Category, n (%)		
≥90%	[redacted]	[redacted]
75–90%	[redacted]	[redacted]
50–75%	[redacted]	[redacted]
<50%	[redacted]	[redacted]

Based on Table 31, CS[3]
CS = company submission; NSCLC = non-small-cell lung cancer; OSAS = Overall Safety Analysis Sets; RET = rearranged during transfection; SAS = Safety Analysis Sets; SD = standard deviation

Table 3.29: Selpercatinib dose modifications (Safety Analysis Sets)

	SAS (*RET* fusion-positive NSCLC; N=356)	**OSAS (overall population; N=796)**
Dose reduction, n (%)		
Any	[redacted]	[redacted]
For AE	[redacted]	[redacted] **(41)**

	SAS (*RET* fusion-positive NSCLC; N=356)	OSAS (overall population; N=796)
For other reason	[redacted]	[redacted]
Dose interruption, n (%)		
Any	[redacted]	[redacted]
For AE	**245 (68.8)**	**510 (64.1)**
For other reason	[redacted]	[redacted]
Dose increase, n (%)		
Any	[redacted]	[redacted]
Intra-patient escalation[a]	[redacted]	[redacted]
Re-escalation[b]	[redacted]	[redacted]
Other reason	[redacted]	[redacted]

[a] Patients started at a lower dose during dose escalation that was subsequently increased
[b] Re-escalation after a dose reduction
AE = adverse event; CS = company submission; NSCLC = non-small-cell lung cancer; OSAS = Overall Safety Analysis Set; RET = rearranged during transfection; SAS = Safety Analysis Sets

Adverse events were graded by the Investigator, when applicable, using the NCI CTCAE.

3.2.8.1.2 Treatment-emergent adverse events

Adverse events were defined to be treatment emergent if they started on or after the date of the first dose of selpercatinib (Study Day 1). For cases where it was not possible to ascertain treatment emergence, the event was classified as treatment emergent.

In the OSAS, 95% of AEs were considered to be related to selpercatinib but the majority were deemed to be of low severity, with 38.6% classed as Grade 3 or Grade 4 (Table 3.30). A similar pattern was observable in the NSCLC SAS. Permanent discontinuation of selpercatinib due to AEs were infrequent (3.1%) in the OSAS, with no predominant pattern among the individual AEs reported. One fatal treatment emergent adverse event (TEAE) within 28 days of last dose was attributed to selpercatinib in the OSAS, and zero deaths related to selpercatinib occurred in the NSCLC SAS.

A high proportion of patients in the OSAS (99.9%) experienced at least one TEAE during treatment. The most common TEAEs, defined as occurring in 15% of patients or more, in the OSAS were: oedema (48.5%), diarrhoea (47.0%), fatigue (45.9%), dry mouth (43.2%), hypertension (41%), aspartate aminotransferase (AST) increase (36.7%), alanine transaminase (ALT) increase (35.7%), constipation (32.8%), abdominal pain (33.7%), rash (32.8%) and nausea (31.2%).[29] The vast majority of AEs were classified as Grades 1–2 and deemed to be clinically manageable in clinical practice. Rates of different TEAEs were broadly similar between the OSAS and NSCLC SAS analysis sets, as presented in Table 3.31.

Table 3.30: Summary of safety trends (Safety Analysis Sets)

	SAS (*RET* fusion-positive NSCLC; N=356)	OSAS (overall population; N=796)
Any TEAE, n (%)		
All	356 (100.0)	795 (99.9)
Related to selpercatinib	341 (95.8)	756 (95.0)
Grade 3 or 4 TEAE, n (%)		
All	263 (73.9)	572 (71.9)
Related to selpercatinib	143 (40.2)	307 (38.6)
TEAE leading to treatment discontinuation, n (%)		
All	34 (9.6)	64 (8.0)
Related to selpercatinib	[redacted]	25 (3.1)
TE-SAE, n (%)		
All	[redacted]	353 (44.3)
Related to selpercatinib	[redacted]	87 (10.9)
Fatal TEAE		
All	[redacted]	45 (5.7)
Related to selpercatinib	[redacted]	1 (0.1)

Based on Table 33, CS[3]
CS = company submission; NSCLC = non-small-cell lung cancer; OSAS = Overall Safety Analysis Set; RET rearranged during transfection; SAE = serious adverse event; SAS = Safety Analysis Set; TEAE = treatment emergent adverse event

Table 3.31: Common TEAEs of all grades (15% or greater in any Safety Analysis Sets)

Preferred term	Maximum severity incidence, n (%)			
	SAS (*RET* fusion-positive NSCLC; N=356)		OSAS (overall population; N=796)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Oedema	178 (50.0)	2 (0.6)	386 (48.5)	6 (0.8)
Diarrhoea	184 (51.7)	15 (4.2)	374 (47.0)	40 (5.0)
Fatigue	153 (43.0)	8 (2.2)	365 (45.9)	25 (3.1)
Dry mouth	163 (45.8)	0 (0.0)	344 (43.2)	0 (0.0)
Hypertension (AESI)	141 (39.6)	68 (19.1)	326 (41.0)	157 (19.7)
AST increased	149 (41.9)	37 (10.4)	292 (36.7)	70 (8.8)

ALT increased	147 (41.3)	[redacted]	284 (35.7)	91 (11.4)
Abdominal pain	101 (28.4)	5 (1.4)	268 (33.7)	20 (2.5)
Constipation	96 (27.0)	5 (1.4)	261 (32.8)	6 (0.8)
Rash	130 (36.5)	4 (1.1)	261 (32.8)	5 (0.6)
Nausea	112 (31.5)	4 (1.1)	248 (31.2)	9 (1.1)
Blood creatinine increased	92 (25.8)	10 (2.8)	227 (28.5)	15 (1.9)
Headache	94 (26.4)	3 (0.8)	220 (27.6)	11 (1.4)
Cough	87 (24.4)	0 (0.0)	184 (23.1)	0 (0.0)
Dyspnoea	84 (23.6)	16 (4.5)	179 (22.5)	25 (3.1)
Vomiting	78 (21.9)	4 (1.1)	178 (22.4)	14 (1.8)
ECG QT prolongation (AESI)	74 (20.8)	21 (5.9)	168 (21.1)	38 (4.8)
Arthralgia	[redacted]	[redacted]	165 (20.7)	2 (0.3)
Back pain	[redacted]	[redacted]	153 (19.2)	12 (1.5)
Dizziness	[redacted]	[redacted]	152 (19.1)	2 (0.3)
Decrease appetite	[redacted]	[redacted]	150 (18.8)	3 (0.4)
Pyrexia	79 (22.2)	1 (0.3)	135 (17.0)	1 (0.1)
Urinary tract infection	70 (19.7)	8 (2.2)	135 (17.0)	12 (1.5)
Thrombocytopenia	74 (20.8)	20 (5.6)	123 (15.5)	24 (3.0)
Dry skin	[redacted]	[redacted]	122 (15.3)	0 (0.0)
Hypocalcaemia	[redacted]	[redacted]	121 (15.2)	22 (2.8)

Based on Table 34, CS[3]
ALT = alanine aminotransferase; AST = aspartate aminotransferase; AESI = adverse event of special interest; CS = company submission; ECG = electrocardiogram; NSCLC = non-small-cell lung cancer; OSAS = Overall Safety Analysis Set; QT = QT interval; RET rearranged during transfection; SAS = Safety Analysis Set; TEAE = treatment-emergent adverse event

3.2.8.1.3 Grade 3–4 treatment-emergent adverse events

In the OSAS, Grade 3 or 4 TEAEs were reported in 572 (71.9%) patients, irrespective of relatedness to study drug (Table 3.32). The most common Grade 3–4 events were hypertension (19.7%), ALT increase (11.4%), and AST increase (8.8%) in the OSAS. Despite the relatively high level of Grade 3–4 TEAEs observed in the OSAS, only a small proportion (307 [38.6%]) were considered by the Investigator to be related to selpercatinib. In the NSCLC SAS, 263 (73.9%) patients experienced Grade 3–4 TEAEs, irrespective of relatedness to selpercatinib (Table 3.32). A smaller proportion (143 [40.2%]) were considered by the Investigator to be related to selpercatinib. Common TEAEs mirrored the OSAS analysis set.

Table 3.32: Grade 3–4 TEAE (occurring in ≥2% of patients)

Preferred term	SAS (*RET* fusion-positive NSCLC; N = 356)		OSAS (overall population; N=796)	
	Any	Related to selpercatinib	Any	Related to selpercatinib
One or more Grade 3–4 AEs	263 (73.9)	143 (40.2)	572 (71.9)	307 (38.6)
Hypertension	68 (19.1)	49 (13.8)	157 (19.7)	105 (13.2)
ALT increased	53 (14.9)	41 (11.5)	91 (11.4)	72 (9.0)
AST increased	37 (10.4)	24 (6.7)	70 (8.8)	50 (6.3)
Lymphopenia	[redacted]	[redacted]	41 (5.2)	NR
Diarrhoea	15 (4.2)	8 (2.2)	40 (5.0)	16 (2.0)
ECG QT prolonged	21 (5.9)	14 (3.9)	38 (4.8)	27 (3.4)
Pneumonia	[redacted]	[redacted]	34 (4.3)	NR
Fatigue	8 (2.2)	3 (0.8)	25 (3.1)	17 (2.1)
Dyspnoea	16 (4.5)	12 (3.6)	25 (3.1)	14 (2.0)
Thrombocytopenia	20 (5.6)	[redacted]	24 (3.0)	0
Anaemia	[redacted]	[redacted]	23 (2.9)	9 (1.3)
Hypocalcaemia	[redacted]	[redacted]	22 (2.8)	2 (0.3)
Pleural effusion	[redacted]	[redacted]	21 (2.6)	2 (0.3)

Based on Table 35, CS[3]
Grade 3–4 AEs related to selpercatinib are reported if occurring in 15% or more of the populations. Grade 3–4 AEs irrespective of their relationship are reported if occurring in 2% or more of the populations.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CS = company submission; ECG = electrocardiogram; NSCLC = non-small cell lung cancer; NR = not reported; OSAS = Overall Safety Analysis Set; QT = QT interval; RET = rearranged during transfection; SAS = Safety Analysis Set; TEAE = treatment-emergent adverse event

3.2.8.1.4. Treatment emergent adverse events of special interest

Based on predictions from the *RET*-related literature, the preclinical toxicology programme and clinical experience with selpercatinib, AEs of special interest were identified for focussed analysis: ALT/AST increase, drug hypersensitivity reaction, hypertension and notable event QT prolongation. These special interest AEs are monitorable and reversible with successful dose modification strategies, which allow the majority of patients who experience these events to continue safely on therapy.

ALT/AST increase

In the OSAS, the TEAE of AST increase was reported in 36.7% patients (28.8% related to selpercatinib; 8.8% Grade 3–4; 6.3% Grade 3–4 and related to selpercatinib). The TEAE of ALT increase was reported in 35.7% of OSAS patients (28.5% related to selpercatinib; 11.5% Grade 3–4; 9.0% Grade 3-4 and related to selpercatinib). The majority of ALT and AST TEAEs were Grade 1 or 2.[29] Although ALT and AST TEAEs were the most common reasons for dose interruptions (ALT = [redacted]%; AST = [redacted]%) and reductions (ALT = [redacted]%; AST = [redacted]%), they led to permanent discontinuation in only [redacted] OSAS patients. In addition, no patients met Hy's Law criteria of drug induced liver injury.

Hypersensitivity

Selpercatinib-related hypersensitivity was defined as patients who, early in their treatment course, experienced a constellation of symptoms or findings inclusive of maculopapular rash that was often preceded by fever and associated with arthralgias or myalgias. These were often followed by platelet decrease and/or transaminase increases or, less commonly, by a blood pressure decrease, tachycardia and/or creatinine increase.

In the OSAS, drug hypersensitivity was observed in a [redacted] of patients who had one or more AE of hypersensitivity. The median time to first onset was [redacted] weeks (range: [redacted]). Grade 3 was the worst severity AE for [redacted] patients ([redacted]) and there were no Grade 4 or above hypersensitivity events. Hypersensitivity was deemed serious (all related to selpercatinib) in [redacted] OSAS patients.[29]

Overall, interventions through dose interruption and dose reduction were successful and, in most cases, patients were able to continue study drug treatment after dose reduction and/or interruption. Of the [redacted] OSAS patients with hypersensitivity reactions, [redacted] patients underwent dose reduction and [redacted] dose interruption. Only [redacted] of the [redacted] patients were reported to permanently discontinue selpercatinib due to a hypersensitivity reaction.

Hypertension

In the OSAS, the AE of hypertension was reported in 41% of patients (28.1% considered related to selpercatinib), with 19.6% classified as Grade 3 and 0.1% classified as Grade 4. Of patients having experienced Grade 3–4 AEs of hypertension 13.2% were considered to be related to selpercatinib. A similar proportion of NSCLC SAS patients experienced hypertension (141 [39.6%]), with 68 (19.1%) classified as Grade 3 and none as Grade 4.[34] Whilst hypertension was frequently reported, it can be managed easily and therefore did not result in substantial dose reductions or treatment interruptions. A minority of OSAS patients required dose interruption ([redacted]) and/or reduction ([redacted]). [redacted] patient discontinued therapy due to an AE of hypertension.

Moreover, of the [redacted] OSAS patients, [redacted] of patients had a reported chronic history of hypertension and [redacted] did not. The frequency of reported hypertension AEs was similar between these patients despite the difference in medical history.

Notable Event-QT prolongation

Any grade ECG QT prolongation was reported for 168 patients (21.1%), with 130 (16.3%) considered related to selpercatinib in the OSAS. The majority of events were Grade 1 or Grade 2. [redacted] had an AE of QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation that was deemed serious. QTcF prolongation was manageable by selpercatinib dose interruptions ([redacted] patients) or reductions ([redacted] patients), while no action with drug was taken in [redacted] patients. No patients discontinued treatment due to QT prolongation in the OSAS.

To date, [redacted] clinically significant TEAE related to QT prolongation such as treatment emergent arrhythmias, ventricular tachycardia, ventricular fibrillation, sudden death or Torsades de Pointes have been observed. QT prolongation events can be managed and reversed with successful dose modification strategies, allowing patients to continue safely on therapy.

Safety conclusions

In LIBRETTO-001, selpercatinib was well tolerated across all tumour types studied. The safety profile was characterised by recognisable toxicities across both the NSCLC SAS and OSAS. These toxicities were easily reversable through dose interruption or addressed through dose reduction or concomitant

medication. Whilst hypertension was frequently reported, it can be managed easily and therefore did not result in substantial dose reductions or treatment interruptions. As a result, permanent discontinuation of selpercatinib due to TEAEs were infrequent (8%), meaning patients could consistently benefit from the highly efficacious anti-tumour activity of selpercatinib. This favourable safety profile is as anticipated given the high specificity of selpercatinib for *RET*.

EAG comment: There are no specific adverse event data for the treatment naïve sub-set (SAS1 dataset). This is a potential problem as it is, as it is not possible to exclude a greater concentration of AEs in this sub-group than are observed overall. This has been deemed a key issue.

3.2.8.2 LIBRETTO-321

Safety was evaluated in all 47 patients with NSCLC. Forty-six (97.9%) had at least one TEAE. Twenty-nine (61.7%) patients had a TEAE of at least Grade 3. The most prevalent TEAEs of at least Grade 3 were increased AST level (21.3%), hypertension (19.1%), increased ALT (17.0%), and thrombocytopenia (17.0%). Treatment emergent adverse events led to discontinuation of the study drug in 3 (6.4%) patients. Two of these - decreased platelet count and abnormal liver function - were deemed related to selpercatinib. The most common TEAEs leading to dose reductions were increased AST (12.8%), hypersensitivity (12.8%), decreased platelet count (8.5%), and increased level of ALT (6.4%). There were no deaths due to TEAEs.

The authors concluded that the data suggest that '*selpercatinib was well tolerated and the safety profile of selpercatinib in Chinese patients with RET altered tumours is consistent with the findings in the global population and East Asians included in LIBRETTO-001.*' [24]

EAG comment: There are no specific AE data for the treatment naïve sub-group (n=8). This is a potential problem as it is it is not possible to exclude a greater concentration of AEs in this sub-group than are observed overall. This has been deemed a key issue.

3.2.8 Ongoing studies

The company stated that additional data from LIBRETTO-001 may become available during the course of the evaluation, based on further data cuts in [redacted].

They also stated that LIBRETTO-431 (NCT04194944) is a randomised, open-label, Phase 3 trial comparing selpercatinib to platinum-based and pemetrexed therapy, with or without pembrolizumab, as initial treatment of advanced or metastatic *RET* fusion-positive NSCLC with results for LIBRETTO-431 expected in December 2023 and that it is not anticipated for any data to become available during the course of this evaluation.

Selpercatinib in RET fusion-positive non-small-cell lung cancer (SIREN) was mentioned as an international multi-centre real world evidence (RWE) study observing the efficacy and safety of selpercatinib in clinical settings in 50 patients with *RET* fusion-positive NSCLC, 13 of which were treatment-naïve.[35] The company stated that current data are immature (median follow-up of 10 months) but further data collection is planned in the future.

The company stated that if selpercatinib was to receive a recommendation for use on the Cancer Drugs Fund (CDF), data would be collected from LIBRETTO-001, LIBRETTO-431 and SIREN during the course of CDF funding.

EAG comment: Randomised controlled trial data in the population of interest i.e., those who are RET fusion-positive, would be much more useful, and so the company has been asked to provide the earliest

date by which an interim analysis from the randomised LIBRETTO-431 trial might be available, and the outcomes that will be presented. The company responded by stating that, "*The interim analysis will be event driven and will be conducted when approximately* [redacted] *events in the primary outcome, PFS by BICR, have been observed in the ITT-pembrolizumab population. It is anticipated this criterion will be met in* [redacted]*, with results expected to be available from* [redacted]."[13] In contrast to the unbiased estimate in the correct population expected from this RCT, the current CS relies on an ITC between the single arm study of LIBRETTO-001 and the single arm of another study, KEYNOTE-189, not in the RET fusion-positive population, with statistical adjustment to reduce bias (see Section 3.4). Therefore, the EAG have identified the lack of RCT data in the correct population as a key issue.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In Section D.2 of the appendices, it was reported that a total of 23,180 publications were identified through electronic database searches. An additional 54 publications were identified via other sources, including grey literature and bibliography searches. As also reported in Section B.2.1 of the CS, following de-duplication of results, 15,819 studies were ultimately screened at the title and abstract stage. Full texts (published articles and conference abstracts) of the remaining 887 records were obtained and assessed for eligibility. A total of 724 records that did not meet the PICOS criteria were excluded. In total, 163 publications reporting on 88 unique trials met the inclusion criteria.

According to the CS, as the first line to progression treatment setting more closely matched the submission decision problem than first line treatments, the company only included studies reporting on 'first line to progression' treatments. As also stated in Section B.2.1 of the CS and D.2 of the appendices, out of the 88 originally eligible trials, a total of 66 first line to progression studies were identified and ultimately included in the clinical SLR. The list of those first line to progression treatments that are relevant to the company's decision problem i.e., KEYNOTE-021, KEYNOTE-189 and KEYNOTE-189 Japan is presented in Table 3.33.[17, 18, 20]

The company also reported in Section D.3 of the appendices and B.2.8.2 of the CS that, based on the SLR, of the 70 studies reported in 77 peer-reviewed publications and 44 conference abstracts included in the clinical SLR up until the July 2021 update, 58 studies reported on "first-line to progression treatments" that fully met the SLR eligibility criteria. However, in Section 2.8.2 and Section D.3 of the appendices[8] it was stated that only 31 could be connected in the NMA network: 31 reported OS, 29 reported PFS data, and 27 studies reported ORR data. Those 31 studies are shown in Table 3.34 with the three that are relevant to the company's decision problem i.e., KEYNOTE-021, KEYNOTE-189 and KEYNOTE-189 Japan in bold and highlighted in green.[17, 18, 20]

Table 3.33: List of the three included studies for SLR of first line to progression clinical trial evidence for selpercatinib and comparators in the decision problem

Study ID	Clinical trial number	Study reference
KEYNOTE-021[a]	NCT02039674	Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *The Lancet Oncology* 2016; 17(11).

Study ID	Clinical trial number	Study reference
		http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/983/CN-01289983/frame.html.
KEYNOTE-189[a]	NCT02578680	Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. New England Journal of Medicine 2018;378(22):2078-92.
KEYNOTE-189 – Japan[a]		Horinouchi H, Nogami N, Saka H, Nishio M, Tokito T, Takahashi T, et al. Pembrolizumab plus pemetrexed-platinum for metastatic nonsquamous non-small-cell lung cancer: KEYNOTE-189 Japan Study. Cancer science. 2021;112(8):3255-65.

Based on Table 26, CS Appendix D[8]
[a] First update (SLR2)
CS = company submission; SLR = systematic literature review

Table 3.34: Summary of studies used to perform the network meta-analysis

Number	Citation(s)	Study ID	Intervention	Outcomes included in NMA
1	Schuette 2017	65Plus	BEVc + PEMc	ORR, PFS, OS
			BEVc + PEMc + PLATi	
2	Zhou 2015	BEYOND	PACi + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
3	Zhou 2021	CameL	CAMRc + PEMc + PLATi	ORR, PFS, OS
			PEMc + PLATi	
4	Hellmann 2018	CheckMate 227	PEMc + PLATi	ORR, PFS, OS
			IPIc + NIVOc	
5	Paz-Ares 2021	CheckMate 9LA	PEMi + PLATi + IPIc + NIVOc	OS, PFS
			PEMc + PLATi	
6	Koyama 2018	CLEAR	BEVc + PEMc + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
7	Doebele 2015	Doebele 2015	PEMc + PLATi + RAMc	ORR, PFS, OS
			PEMc + PLATi	
8	Sezer 2021	EMPOWER-Lung 1	CEM	PFS, OS
			(GEMi or PACi or PEMc) + PLATi	
9	Galetta 2015	ERACLE	PEMc + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
			Nab-PACi + PLATi	
10	West 2019	IMPower 130	ATEZ + CARB + PAC ATEZ + (maintenance)	ORR, PFS, OS
			CARB + PAC + (BSC or PEM) (maintenance)	
11		IMPower132	PEMc + PLATi	ORR, PFS, OS

Number	Citation(s)	Study ID	Intervention	Outcomes included in NMA
	Nishio 2021		ATEZc + PEMc + PLATi	
12	China, Lu 2021	IMPower132	ATEZc + PEMc + PLATi	ORR, PFS, OS
			PEMc + PLATi	
			ATEZc + BEVc + PACi + PLATi	
13	Socinski 2018	IMPower150	ATEZ + BEV + CARB + PAC ATEZ + (maintenance) + BEV(maintenance)	ORR, PFS, OS
			BEV + CARB + PAC + BEV (maintenance)	
			ATEZ + CARB + PAC + ATEZ (maintenance)	
14	Johnson 2004	Johnson 2004	BEVc + PACi + PLATi	ORR, OS
			PACi + PLATi	
15	Karayama 2016	Karayama 2016	BEVc + PEMc + PLATi	PFS, OS
			BEVi + PEMc + PLATi	
16	**Langer 2016**	**KEYNOTE-021**	**PEMc + PLATi**	**ORR, PFS, OS**
			PEMc + PEMBROc + PLATi	
			PEMBRO	
			(CARB + PEM) or (CIS + PEM) or (CARB + GEM) or (CIS + GEM) or (CARB + PAC) + PEM (maintenance)	
17	**Gandhi 2018**	**KEYNOTE-189**	**PEMc + PEMBROc + PLATi**	**ORR, PFS, OS**
			PEMc + PLATi	
18	Wu 2020	KEYNOTE-042 China	PEMc + PLATi	OS
			PEMBROc	
			PEMc + PLATi	
19	**Horinouchi 2021**	**KEYNOTE-189 Japan**	**PEMc + PLATi**	**ORR, PFS, OS**
			PEMc + PEMBROc + PLATi	
			PEMBROc	
20	Lee 2016	Lee 2016	PEMc + PLATi	ORR, PFS, OS
			PEMc	
21	LIBRETTO-001	LIBRETTO-001	SELc	ORR, PFS, OS
			PEMc + PLATi	
22	Fukuda 2019	LOGIK1201	BEVc + PEMc	ORR, PFS, OS
			PEMc	
23	Spigel 2018	Spigel 2018	BEVc + PEMc	ORR, PFS, OS
			PEMc	
			BEVc + PEMc + PLATi	

Number	Citation(s)	Study ID	Intervention	Outcomes included in NMA
24	Yang 2020	ORIENT-11	SINTc + PEMc + PLATi	ORR, PFS, OS
			PEMc + PLATi	
25	Socinski 2012	Socinski 2012	Nab-PACi + PLATi	ORR, PFS, OS
			PACi + PLATi	
26	Niho 2012	Niho 2012	PACi + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
27	Patel 2013	PointBreak	BEVc + PEMc + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
28	Zinner 2015	PRONOUNCE	PEMc + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
29	Lu 2021	RATIONALE 304	PEMc + PLATi	ORR, PFS, OS
30	Sandler 2006	Sandler 2006	PACi + PLATi	ORR, PFS, OS
			BEVc + PACi + PLATi	
31	Sugawara 2021	TASUKI-52	BEVc + PACi + PLATi	ORR, PFS, OS
			NIVOc + BEVc + PACi + PLATi	

Based on Table 27, Appendices.[8]
ATEZ = atezolizumab; BEV = bevacizumab; c = continuous; CAMR = camrelizumab; CARB = carboplatin; CIS = cisplatin; ERL = erlotinib; GEF = gefitinib; GEM = gemcitabine; I = induction; ID = identification; IPI = ipilimumab; m = maintenance; nab-PAC = nab-paclitaxel; NMA = network meta-analysis; NIVO = nivolumab; ORR = objective response rate; OS = overall survival; PAC = paclitaxel; PCB = placebo; PEM = pemetrexed; PEMBRO = pembrolizumab; PLAT = platinum chemotherapy; PFS = progression-free survival; RAM = ramucirumab

3.3.1 Characteristics of comparator studies included in decision problem

The three studies, KEYNOTE-021, KEYNOTE-189 and KEYNOTE-189 Japan in bold and highlighted in green, that are relevant to the decision problem were all in non-squamous histology and ECOG performance status 0 or 1 with baseline characteristics shown in Tables 3.35 and 3.36.[17, 18, 20] The baseline characteristics of the other studies in the NMA have not been summarised here given that they were not necessary for the estimation of the treatment effect between selpercatinib and either pemetrexed plus platinum chemotherapy (estimated using the ITC) or pembrolizumab plus pemetrexed plus platinum chemotherapy (see Section 3.4.1 and network diagrams in Section 3.4.2). Note also that Tables 3.35 and 3.36 also contain information on LIBRETTO-001 for comparison. A comparison is also presented of the subset of characteristics (age, sex, ECOG performance status, smoking status, race and stage) in Section 3.4.1, and only with the pemetrexed plus platinum chemotherapy arm of KEYNOTE-189. The company considered that all three of the studies were comparable enough to be included in the NMA, although the company did identify sources of heterogeneity across all 31 studies in the NMA, which prompted a meta-regression (see Section 3.4.2.3).

Table 3.35: Baseline characteristics 1

Trial name, Primary Author, Year	Intervention	N randomised / ITT	Baseline pop.	Mean age (years)	Female		White		Black		Asian		Other race		Hispanic		Smoking status (%)	
					n	%	n	%	n	%	n	%	n	%	n	%	Never	Current or previous
LIBRETTO-001, SAS1	SEL	69	69	63.0 median	43	62.3	48	69.6	4	5.8	13	18.8	4	5.8	-	-	48	69.6
KEYNOTE-021, Langer 2016	PEMBRO + PEM + CARB + PEM (maintenance)	60/60	60	61.8	38	63	49	82	4	7	5	8	2	3	-	-	25	75
	PEM + CARB + PEM optional (maintenance)	63/63	63	63.2	37	59	58	92	0	0	5	8	0	0	-	-	14	86
KEYNOTE-189, Gandhi 2018	PEM + (CARB or CIS) + PEMBRO	410	410	65.0 median	156	38	-	-	-	-	-	-	-	-	-	-	11.7	88.3
	PEM + (CARB or CIS)	206	206	63.5 median	97	47.1	-	-	-	-	-	[redacted]	-	[redacted]	-	-	12.1	87.9
KEYNOTE-189 - Japan, Horinouchi 2021	PEM + (CARB or CIS) + PEMBRO	25/25	25	-	-	-	-	-	-	-	-	-	-	-	-	-	28	72
	PEM + (CARB or CIS)	15/15	15	-	-	-	-	-	-	-	-	-	-	-	-	-	20	80

Based on Table 32, Appendices and Ghandi;[8, 17] Table 3.12 for LIBRETTO-001
CARB = carboplatin; CIS = cisplatin; ITT = intention to treat; PEM = pemetrexed; PEMBRO = pembrolizumab; SEL = selpercatinib

Table 3.36: Baseline characteristics 2

Trial Name, Primary Author, Year	Intervention	Baseline population	Histology								ECOG/WHO performance status						AJCC stage			
			Non-squamous NSCLC		Adeno-carcinoma		Large cell		Adeno-squamous carcinoma		0		1		2		IIIB		IV	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
LIBRETTO-001, SAS1	SEL	69	69	100	62	89.9	0	0	-	-	25	36.2	40	58.0	4	5.8	3	4.2	50	91.3
KEYNOTE-021, Langer 2016	PEMBRO + PEM + CARB + PEM (maintenance)	60	60	100	58	97	0	0	-	-	24	40	35	58	-	-	1	2	59	98
	PEM + CARB + PEM optional (maintenance)	63	63	100	55	87	1	2	-	-	29	46	34	54	-	-	2	3	60	95
KEYNOTE-189, Gandhi 2018	PEM + (CARB or CIS) + PEMBRO	410	410	100	394	96.1	5	-	-	-	186	45.4	221	53.9	1	0.2	-	-	-	-
	PEM + (CARB or CIS)	206	206	100	198	96.1	2	-	2	-	80	38.8	125	60.7	0	0	-	0.5	-	99.5
KEYNOTE-189 - Japan, Horinouchi 2021	PEM + (CARB or CIS) + PEMBRO	25	-	-	23	92	-	-	-	-	15	60	10	40	-	-	-	-	-	-
	PEM + (CARB or CIS)	15	-	-	14	93	-	-	-	-	9	60	6	40	-	-	-	-	-	-

Based on Table 33, Appendices and Ghandi 2018;[8, 17] Tables 3.12 and 3.13 and Drilon 2020 for LIBRETTO-001[36]
AJCC = American Joint Committee on Cancer; CARB = carboplatin; CIS = cisplatin; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small-cell lung cancer; PEM = pemetrexed; PEMBRO = pembrolizumab; SAS1 = Supplemental Analysis Set 1; SEL = selpercatinib; WHO = World Health Organization

EAG comment:

- There is a mismatch between sections of the appendices and the CS in reported numbers of papers included in the SLR and therefore that were eligible for the NMA. In Section B.2.1 of the CS and D.2 of the appendices[8] (see Table 3.33), 66 first line to progression studies are listed, but in Section B.2.8.2 of the CS[3] and Section D.3 of the appendices 58 first-line to progression studies are mentioned, from which 31 are included in the NMA. The source of the extra eight studies is unclear but it is probably due to the updated search in April 2022 not retrieving any studies that the company thought relevant to the NMA: "*As the April 2022 SLR update did not identify any further studies that would be informative to the NMA relevant to this decision problem, studies up to the July 2021 update were assessed for inclusion in the NMA".* Nevertheless, it remains unclear to the EAG by which criteria these eight studies were deemed uninformative.
- Although not explicitly stated, it appears that all three studies that compared pembrolizumab plus pemetrexed plus platinum chemotherapy to pemetrexed plus platinum chemotherapy were included in the NMA to indirectly estimate the treatment effect of the former versus selpercatinib given that an ITC was used to estimate the treatment effect of the latter versus selpercatinib. This means that any heterogeneity and trial selection for pooling will have implications for the comparison between selpercatinib and the pembrolizumab combination.
- The most obvious source of heterogeneity is that all LIBRETTO-001 patients were RET fusion-positive and RET fusion status is unknown in the three comparator trials: the implications of this are explored further in Section 3.4.1.5, as are those of other baseline characteristics in terms of what might be a treatment effect modifier or prognostic in the context of the ITC. It is also the case that KEYNOTE-189 Japan is as study of only Japanese patients, which also might limit its applicability.

The implications of any heterogeneity are discussed in Section 3.4.2.4.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Indirect treatment comparison

A NMA was performed to compare the efficacy of selpercatinib to other first line treatments relevant to the decision problem for the outcomes of ORR, PFS and OS (see Section 3.4.2). However, LIBRETTO-001 was a single-arm trial and therefore did not compare the efficacy of selpercatinib in advanced RET fusion-positive NSCLC directly to comparators relevant to the decision problem. To connect selpercatinib to the NMA, the company chose to first conduct an ITC between selpercatinib and pemetrexed plus platinum chemotherapy. This entailed the use of IPD from LIBRETTO-001 selpercatinib arm and the pemetrexed plus platinum chemotherapy arm from the KEYNOTE-189 RCT using propensity score matching (PSM) to account for any differences between trial populations. The company referred to this ITC as the "*generation of [a] pseudo-comparator arm*". Results are given in Section 3.4.2.

EAG comment:

- No justification was provided as to why pemetrexed plus platinum chemotherapy was chosen for the ITC, as opposed to any of the other comparators in the NICE scope or the NMA. Therefore, the EAG requested this as well as an ITC for each of the comparators in the scope. The company response to the clarification letter was, "*As explained in Section B.2.8.1 of the Company Submission, an ITC using IPD of ORR, PFS and OS with only pemetrexed and platinum chemotherapy was conducted using data from the KEYNOTE-189 trial given that it was the only trial for which the necessary IPD were available. Furthermore, Lilly only had permission and access from the third-*

party holder to these data from the KEYNOTE-189 trial for this arm of the study, and thus a comparison with pembrolizumab with pemetrexed and platinum chemotherapy, or any other comparator in the network or scope, could not be conducted… As outlined above, performing an ITC using IPD of the outcomes with all other comparators in the scope is not possible given that IPD data for comparators other than pembrolizumab with pemetrexed and platinum chemotherapy from the KEYNOTE-189 trial are not available." The EAG is concerned that the rationale for the choice of comparator is an administrative reason rather than one that would make the use of other comparators inappropriate.

- The PSM was the method of adjustment for confounding employed in the ITC. Although the company referred to NICE Technical Support Document (TSD) 17, no justification was provided for its choice. Therefore, the EAG requested that NICE TSD 17 be referred to in assessing which are the best methods for adjusting for confounding and perform at least one other type of adjustment for confounding. In fact, no details of the ITC were provided and so the company was also asked to state the nature of the treatment effect being estimated, ATE or ATT and to provide a full technical report with completion of the QuEENS checklist as recommended in NICE TSD 17.[37] The company response to the clarification letter was "*In line with the recommendations provided in NICE TSD17, in addition to PSM, other methods of control arm adjustment were explored, included genetic matching, propensity score weighting (PSW) using a generalised boosted model, and PSW using a logistic regression model. Guidance provided in NICE TSD17 informed the adjustment techniques."*[13] The results of the adjustment techniques explored in the company's response to clarification are provided below.

3.4.1.1 Propensity score matching

This was the default method for matching the pseudo-comparator arm to the selpercatinib arm, which generated results presented in the CS. The IPD from both trials was used to adjust for between-trial differences in observed baseline characteristics known to have an impact on prognosis (see Table 3.37 below) and to assess outcomes in a matched population. The programming code used for the matching process was provided in the clarification letter. The results of the PSM process are provided below. Covariate balance is illustrated in Figure 3.6 below.

Table 3.37: Baseline characteristics of KEYNOTE-189 before and after PSM

Characteristic	SELc (N=[redacted])	Before PSM[a]	After PSM[a]
		PEMc + PLATi (N=[redacted])	PEMc + PLATi (N=[redacted])
Age (mean, years)	[redacted]	[redacted]	[redacted]
ECOG performance status = 1, %	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]
Race: Other[b], %	[redacted]	[redacted]	[redacted]
Stage III, %	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]

Based on Table 9, Company response to clarification letter[13]
a The analysis followed greedy matching algorithm
b Race: other includes non-white, non-Asian and unknown
c = continuous; ECOG = Eastern Cooperative Oncology Group; i = induction; PEM = pemetrexed; PEMBRO = pembrolizumab; PSM = propensity score matching; SEL = selpercatinib

Figure 3.6. Standardised differences and variance ratio plot before and after propensity score matching

Based on Figure 1, Company response to clarification letter.[13]

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process described above to obtain significance tests for the estimated treatment effect, estimate hazard ratios (HRs) and 95% credible intervals (CrIs) for selpercatinib versus the pseudo-control arm (Table 3.38).

The KM curves for PFS and OS after PSM are presented in Figure 3.7.

Table 3.38. Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via PSM

Endpoint	Hazard ratio (95% CrI)	P value
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Based on Table 10, Company response to clarification letter[13]
CrI = credible interval; OS = overall survival; PFS = progression-free survival; PSM = propensity score matching

Figure 3.7: Kaplan-Meier charts for PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following PSM

Based on Figure 2, Company response to clarification letter[13]

Solid lines represent the survival data (control arm is matched by prognostic factors: age, the proportion of female patients, the proportion of patients who never smoked, ECOG performance status, race, and stage at diagnosis). Shaded portions represent 95% CI.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; SCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PSM = propensity score matching

3.4.1.2 Genetic matching

Genetic matching uses a genetic search algorithm to find a set of weights for each covariate such that optimal balance is achieved after matching. For this analysis, models were conducted using R 3.6.0 for Linux. The programme code was provided in the response to clarification letter.

The results of the genetic matching approach are provided in Table 3.39 below. Covariate balance is illustrated in Figure 3.8.

Table 3.39: **Baseline characteristics of KEYNOTE-189 before and after genetic matching**

Characteristic	SELc (N=[redacted])	Before genetic matching	After genetic matching
		PEMc + PLATi (N=[redacted])	PEMc + PLATi (N=[redacted])
Age (mean, years)	[redacted]	[redacted]	[redacted]
ECOG performance status = 1, %	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]
Race: Other[a], %	[redacted]	[redacted]	[redacted]
Stage III, %	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]

Based on Table 11, Company response to clarification letter[13]
[a] Race: other includes non-white, non-Asian and unknown
c = continuous; ECOG = Eastern Cooperative Oncology Group; i = induction; PEM = pemetrexed; PLAT = platinum chemotherapy; SEL = selpercatinib

Figure 3.8. Standardised differences and variance ratio plot before and after genetic matching

Based on Figure 3, Company response to clarification letter.[13]

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the genetic matching process described above to obtain significance tests for the estimated treatment effect, estimate HRs and 95% CIs for selpercatinib versus the pseudo-control arm (Table 3.40).

The KM curves for PFS and OS after genetic matching are presented in Figure 3.9.

Table 3.40: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via genetic matching

Endpoint	Hazard ratio (95% CrI)	P value
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Based on Table 12, Company response to clarification letter[13]
CrI = credible interval; OS = overall survival; PFS = progression-free survival

Figure 3.9: Kaplan-Meier charts for PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following genetic matching

Based on Figure 4, Company response to clarification letter[13]
Footnote: Solid lines represent the survival data (control arm is matched by prognostic factors: age, the proportion of female patients, the proportion of patients who never smoked, ECOG performance status, race, and stage at diagnosis). Shaded portions represent 95% CI.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; PFS = progression-free survival; NSCLC = non-small-cell lung cancer; OS = overall survival

3.4.1.3 Propensity score weighting using a generalised boosted model

Propensity score weighting (PSW) using a generalised boosted model was conducted using the "twang" package. The programme code used for the weighting process is provided in the clarification letter.

The results of the PSW using a generalised boosted model adjustment process are provided below. Propensity score weighting by generalised boosted model was implemented with two methods of measuring and summarising balance across pre-treatment variables. These were mean effect size (es.mean) and maximum of Kolmogorov-Smirnov statistic (ks.max). They resulted in almost identical balancing results (Table 3.41). However, it should be highlighted that the effective sample size in the resultant pseudo-control arm (PEMc plus PLATi) was smaller than when a matching technique was utilised, making the comparison between arms less powerful.

Table 3.41: Baseline characteristics of LIBRETTO-001 and KEYNOTE-189 before and after PSW using generalised boosted model

Characteristic	SELc (N=[redacted])	Before PSW	After PSW[a]	
		PEMc + PLATi N=206	PEMc + PLATi N_{eff}=50[b]	PEMc + PLATi N_{eff}=50[c]
Age (mean, years)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status = 1, %	[redacted]	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]	[redacted]
Race: Other, %	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	SELc (N=[redacted])	Before PSW	After PSW[a]	
		PEMc + PLATi N=206	PEMc + PLATi N_{eff}=50[b]	PEMc + PLATi N_{eff}=50[c]
Stage III, %	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 13, Company response to clarification letter[13]
[a] The control arm created by propensity score weighting with generalised boosted model algorithm using two methods of measuring and summarising balance across pre-treatment variables; [b] mean effect size (es.mean); [c] maximum of Kolmogorov-Smirnov statistic (ks.max)
c = continuous; ECOG = Eastern Cooperative Oncology Group; i = induction; N = sample size; N_{eff} = effective sample size; PEM = pemetrexed; PLAT = platinum chemotherapy; PSW = propensity score weighting; SEL = selpercatinib

Figure 3.10. Standardised differences and variance ratio plot before and after PSW using generalised boosted model

Based on Figure 5, Company response to clarification letter[13]
es.mean = mean effect size; ks.mean = maximum of Kolmogorov-Smirnov statistic; PSW = propensity score weighting

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process described above to obtain significance tests for the estimated treatment effect, estimate HRs and 95% CIs for selpercatinib versus the pseudo-control arm (Table 3.42).

The KM curves for PFS and OS after PSW by generalised boosted model are provided in Figure 3.11.

Table 3.42: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via PSW using generalised boosted model

Endpoint	Hazard ratio (95% CI)	P-value
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Endpoint	Hazard ratio (95% CI)	P-value
Based on Table 14, Company response to clarification letter[13] CI = confidence interval; OS = overall survival; PFS = progression-free survival; PSW = propensity score weighting		

Figure 3.11: Kaplan-Meier charts for PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following PSW using generalised booster model

Based on Figure 6, Company response to clarification letter[13]
Footnote: Solid lines represent the survival data (control arm is matched by prognostic factors: age, the proportion of female patients, the proportion of patients who never smoked, ECOG performance status, race, and stage at diagnosis). Shaded portions represent 95% CI.
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small-cell lung cancer; PFS = progression-free survival; PSW = propensity score weighing; OS = overall survival

3.4.1.4 PSW using a logistic regression

Propensity score weighting using a logistic regression model was conducted using the "arm" package which utilises the nearest neighbourhood matching procedure. The programme code used for the weighting process was provided in the clarification letter response.[13]

A comparison of baseline characteristics before and after PSW using logistic regression is presented in Table 3.43. After applying PSW using logistic regression, baseline characteristics were between the selpercatinib and pemetrexed plus platinum chemotherapy arms were closer aligned (Figure 3.12). Similar to PSW when using a generalised boosted model, the effective sample size in the resultant pseudo-control arm (PEMc plus PLATi) was smaller than when PSM was utilised, making the comparison between arms less powerful.

Table 3.43: Baseline characteristics of LIBRETTO-001 and KEYNOTE-189 before and after PSW using logistic regression

Characteristic	SELc (N=[redacted])	Before PSW[a]	After PSW[a]
		PEMc + PLATi N=206	PEMc + PLATi N_{eff}=31
Age (mean, years)	[redacted]	[redacted]	[redacted]

Characteristic	SELc (N=[redacted])	Before PSW[a]	After PSW[a]
		PEMc + PLATi N=206	PEMc + PLATi N_{eff}=31
ECOG performance status = 1, %	[redacted]	[redacted]	[redacted]
Female, %	[redacted]	[redacted]	[redacted]
Never smoked, %	[redacted]	[redacted]	[redacted]
Race: Asian, %	[redacted]	[redacted]	[redacted]
Race: Other, %	[redacted]	[redacted]	[redacted]
Stage III, %	[redacted]	[redacted]	[redacted]
Stage IV, %	[redacted]	[redacted]	[redacted]

Based on Table 15, Company response to clarification letter[13]
[a] The analysis followed greedy match as a matching algorithm
c =continuous; ECOG = Eastern Cooperative Oncology Group; i = induction; N = sample size; N_{eff} = effective sample size; PEM = pemetrexed; PLAT = platinum chemotherapy; PSW = propensity score weighting; SEL = selpercatinib

Figure 3.12. Standardised differences and variance ratio plot before and after PSW using logistic regression

[redacted]

Based on Figure 7, Company response to clarification letter[13]
PSW = propensity score weighting

For the outcomes of PFS and OS, non-parametric log-rank test and Cox regression models were performed on the resultant data from the propensity score matching process described above to obtain significance tests for the estimated treatment effect, estimate HRs and 95% CIs for selpercatinib versus the pseudo-control arm (Table 3.44).

The KM curves for PFS and OS after reweighting by PSW using logistic regression are presented in Figure 3.13.

Table 3.44: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (pseudo-control arm) generated via PSW using logistic regression

Endpoint	Hazard ratio (95% CI)	P-value
PFS	[redacted]	[redacted]

Endpoint	Hazard ratio (95% CI)	P-value
OS	[redacted]	[redacted]

Based on Table 16, Company response to clarification letter.[13]
CI = confidence interval; OS = overall survival; PFS = progression-free survival; PSW = propensity score weighting

Figure 3.13. PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following PSW using logistic regression

[redacted]

Based on Figure 8, Company response to clarification letter[13]
NSCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PSW = propensity score weighting

3.4.1.5 ITC Conclusion

The company stated that: "*A clear preference for the selection of an adjustment technique could not be made based on balanced patient characteristics and available estimates alone. PSM was ultimately selected for the adjustment process as the results were associated with the highest external validity; the modelled median PFS and OS were most closely aligned to those observed in KEYNOTE-189 trial for the pemetrexed plus platinum chemotherapy arm. In addition, utilisation of a PSM approach resulted in the most conservative estimates of treatment effect: the PSM approach resulted in the highest median PFS and OS estimates for the pemetrexed plus platinum chemotherapy* arm [see Table 3.43]. *This result is externally valid since, as outlined in response to question B.17a) below, patients in the SAS1 population of the LIBRETTO-001 trial were typically younger and healthier than the advanced NSCLC more generally. As a result, the mean age and number of non-smokers for the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial were anticipated to be artificially reduced in the adjustment process, thus resulting in increased mPFS and mOS for this population."*[13]

Table 3.45: Comparison of the modelled landmark survival estimates, mPFS and mOS generated via the different adjustment methods to the observed values from KEYNOTE-189 for the pemetrexed plus platinum chemotherapy arm

Adjustment method	Month 6	Month 12	Month 18	mPFS (months)	Month 6	Month 12	Month 18	mOS (months)
PSM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genetic matching	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adjustment method	Month 6	Month 12	Month 18	mPFS (months)	Month 6	Month 12	Month 18	mOS (months)
PSW using generalised booster model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSW using logistic regression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KEYNOTE-189 (observed)	-	-	-	4.9				10.6

Based on Table 17, Company response to clarification letter[13]
mPFS = median PFS; mOS = median OS; PSM = propensity score matching; PSW = propensity score weighting

EAG comment: KEYNOTE-189 was used as the source of data for the ITC, although no justification for its choice, as opposed to any other trial, was provided in the CS.[3, 17] Also, the populations were sufficiently different to make sufficient overlap impossible for some variables (e.g., those who "never smoked" comprised [redacted] of the selpercatinib cohort but only [redacted] of the propensity-score-matched pemetrexed plus platinum chemotherapy plus placebo cohort). The company were therefore asked to justify its choice and, if it is not demonstrated to be unequivocally better than those, then to perform an ITC using each of those other data sources using either and individual patient data method according to the NICE TSD 17 or a population adjustment method according to NICE TSD 18. The company response to this request in the clarification letter was, "*..., as noted in the response Question A.21) above, the pemetrexed and platinum chemotherapy arm of the KEYNOTE-189 trial was the only arm with available IPD. For this reason, it was utilised to inform the comparator arm. An IPD method was chosen over a population adjusted method, such as a matching-adjusted indirect comparison (MAIC) described in NICE DSU 18, because the insufficient data on outcomes would mean that the latter would create greater bias and cause methodological difficulties. In addition, a MAIC would adjust for population 'moments' only, whereas utilisation of an IPD adjustment method allows patients to be matched based on individual baseline characteristics. Owing to the large imbalances in certain baseline characteristics caused by RET fusion positive NSCLC patients typically being a younger and healthier demographic than typical lung cancer patients, the use of a population adjusted method would greatly reduce the size of the LIBRETTO-001 dataset (n=69). This would lead to increased uncertainty in the results of the ITC. Additionally, this imbalance of key prognostic factors, such as the low percentages of female and Asian patients, is notable in other pemetrexed plus platinum-based chemotherapy trials identified in the NMA, as presented in Table 18* [in clarification letter response]. *Using summary data would have introduced the additional issue of missing baseline data that may not be reported from publications, such as data that included patients who had never smoked. In addition, there were no other trials which reported any data on patients with specifically RET fusion-positive NSCLC. For these reasons, use of a population adjusted approach was not considered appropriate, and as such, alternative ITC approaches were not conducted*."[13] The EAG consider that, in accordance with NICE TSD 17 and NICE TSD 18, an approach that uses IPD to adjust for confounding is ceteris paribus superior to a method that uses population adjustment.[37, 38] It is also useful that the only trial, KEYNOTE-189, to which the company had access, included a comparison with the only other comparator in the decision problem. As discussed in Section 3.1.2, it might also be that this is one of only three trials that included pemetrexed as recommended in the NG122 and as it would be administered in NHS clinical practice i.e., at induction and maintenance, which the company describe as 'treat to progression'. Another one of the three included trials that could have been considered for the ITC is KEYNOTE-021,

which seems to have baseline characteristics that might be similar those of KEYNOTE-189 (See Section 3.3.1)[17, 20] although the necessary IPD data did not seem to have been available from any of the other included studies. However, as stated in Section 2.3, the EAG is not convinced that these should be the only comparators, which might mean that an ITC versus one of the other comparators in the scope might have been appropriate. Choice of trial data for the ITC therefore is a key issue.

In addition to the 142 patients excluded from the KEYNOTE-189 cohort, five patients were removed from the SAS1 dataset (n=69) to facilitate propensity matching. The reasons were ECOG performance status = 2 ([redacted]) and missing stage data ([redacted]). Removal of participants is a necessary part of propensity-matching. However, in this case it appears that 4/5 excluded from the SAS1 dataset were those with the poorest ECOG score, which could lead to a spurious benefit to be observed for the study drug. The company were asked to state whether the decisions on exclusions in the SAS1 database were made pre-hoc. If so, the company were asked to explain the decision-making process underlying the pre-hoc exclusion strategy. The company responded by stating that, *"Lilly can confirm that the decision on patient eligibility was made pre-hoc before the matching/weighting approaches were attempted. The reason for this pre-hoc decision on exclusion from the SAS1 database being made was that the KEYNOTE-189 study had an inclusion criterion to enrol only patients with an ECOG performance score of 0 or 1. Therefore, it would not be possible to find patients from the KEYNOTE-189 trial who matched the [redacted] patients with an ECOG score of 2 in the SAS-1 population of the LIBRETTO-001 trial.*"[13] The EAG are satisfied with this response.

The EAG opinion is that PSM (the default method used in the base-case) does appear to provide the most conservative results for OS and PFS, out of the methods that were explored. However, it is possible that other methods of adjusting for confounding, not explored by the company, may have generated evidence that would have provided even more conservative results than were produced by PSM (the base-case method). Ultimately, the most appropriate method is the one producing the best reduction in bias, which, assuming selection on observables, is the one that produces the best balance of baseline characteristics. All methods explored produced some discrepancies between the arms. *Propensity score matching* led to large between-arm differences for 'never smoked' and both race variables, *genetic matching* led to some between-arm differences for ECOG and 'race other', while *PSW – generalised boosted* led to differences for female and 'race other', and *PSW – logistic regression* led to differences for female, 'never smoked' and 'race'. Overall, it is difficult to judge which of these methods is the best on that basis. However, it is still possible that other methods (that were not explored) may have been able to demonstrate superior balance to these methods. One possibility suggested in NICE TSD 17 if balance is still not good after matching is the addition of multivariate regression on the matched sample.[37] If so, the results from such an unexplored method may have been preferable. Such a preferable method might produce results that demonstrate less of a benefit for selpercatinib than observed in the base-case, implying that the base-case results may be over-estimating the benefits of selpercatinib.

It was also unclear how covariates/baseline characteristics were selected as potential treatment effect modifiers or prognostic. The EAG requested a full description of the method and the company responded by providing the results of a separate SLR in Appendix C of the clarification letter response in the form of a large table that listed the studies that found any one of a number of variables to be prognostic and in which direction.[13] Unfortunately, there was no evidence presented as to how this large table was used to identify the final list of six variables (age, sex, race, smoking status, ECOG performance status, disease stage). Notable omissions of potential prognostic factors were lower weight (all studies showed associated with worse prognosis) and prior therapy (many studies, but complex relationship). Brain metastases were also associated with worse prognosis, having been identified as prognostic in the CS,[3] and having potential for treatment effect modification as revealed

by subgroup analysis of LIBRETTO-001 (see Section 3.2.6). Although the sub-group differences were non-significant, statistical significance/ non-significance is not informative in an analysis that is not sufficiently powered, and the EAG believes, in view of the large differences in point-estimates that there is a possibility of a type II error. Non-squamous histology seemed to confer better prognosis, but studies were selected on that basis anyway. No mention was made of RET fusion status, and this might be because the company had already determined that it was not prognostic: *"Adjustments relating to the presence of RET fusion were not made, due to the inconclusive prognostic nature of a RET fusion, as described in Section B.1.2.1."* (page 72).[3] The EAG notes that Section B.1.2.1 does contain a discussion of the evidence on the prognostic nature of RET fusion status, which suggests that RET fusion-positive is associated with better prognosis. However, it also seems to be associated with characteristics that might confer better prognosis such as younger age, non-smoking status, and better ECOG performance status, as shown in one observational study.[39] The company cited that study's conclusion that any advantage in OS, which had been statistically significant, no longer was after adjusting for baseline characteristics (age, sex, race, practice type (academic or community), body weight, body mass index (BMI), stage at initial diagnosis, tumour histology, smoking status, microsatellite instability (MSI) status, genomic alterations, ECOG performance status, PD-L1 expression (positive = >1% staining versus negative), initial treatment regimen (checkpoint inhibitor use yes/no), and reported metastatic sites). However, the EAG notes that the HR point estimate still favoured RET fusion-positive and that the 95% CI only just crossed 1 (1.52 (0.95, 2.43), p = 0.08), which might be due to the very small number of RET fusion-positive patients (n=46) and the large number of covariates (n=15). Therefore, it seems that RET-fusion status should at least have been considered for adjustment or patient selection. Most worryingly, an editorial in the Annals of Oncology concluded: *"After reviewing current data on selpercatinib* [LIBRETTO-001] *and comparing them with standard care in NSCLC, we have concluded that, while promising, the drug needs to be investigated in an RCT."*[40] This was partly on the basis of the findings of a retrospective analysis of 19 stage IIIB/IV lung adenocarcinoma patients with RET rearrangements treated with pemetrexed with or without combination therapy.[41] This study showed a PFS of 19 months (95% CI 12–not reached), very similar to that for selpercatinib in LIBRETTO-001 (21.95 months (95% CI: 13.8–NE) months). Of course, the EAG acknowledge that this is only one very small low-quality study not obtained by systematic review, but it does highlight the potential problem of lack of comparative evidence in the RET fusion-positive population.

In summary, the high risk of bias in a non-randomised between study comparison, the continued lack of balance of covariates and the possible omission of consideration of important prognostic covariates, including RET fusion status, constitutes a key issue.

3.4.2 Network meta-analysis (NMA)

3.4.2.1 NMA Methodology

For the NMA, both random effects and fixed effects models were assessed for all outcomes and the model which best fitted the data were used; in the base-case a random effects model was selected for all outcomes.

Only results from the NMA for the comparison with pembrolizumab with pemetrexed plus platinum chemotherapy and pemetrexed plus platinum chemotherapy were provided, although the NMA included more comparators, the reason provided by the company being that it was to support Health Technology Appraisal (HTA) processes in multiple countries.

Network diagrams were presented and are shown in Figures 3.14 to 3.16.

Figure 3.14: Network diagram for treatments included in the NMA for ORR

Based on Figure 13, CS[3]

ATEZ = atezolizumab; BEV = bevacizumab; c =continuous; CAMR = camrelizumab; CEMIPL = cemiplimab; CrI = credible intervals; CS = company submission; DURV = durvalumab; GEM = gemcitabine; HR = hazard ratios; i = induction; IPI = ipilimumab; Nab-PAC = nab-paclitaxel; NMA = network meta-analysis; NIVO = nivolumab; ORR = overall response rate; PAC = paclitaxel; PEM = pemetrexed; PEMBRO = pembrolizumab; PLAT = platinum chemotherapy; RAM = ramucirumab; RE = random-effects; SEL = selpercatinib; SINT = sintilimab; TISL = tislelizumab

Figure 3.15: Network diagram for treatments included in the NMA for PFS

Based on Figure 15, CS[3]

ATEZ = atezolizumab; BEV = bevacizumab; c =continuous; CAMR = camrelizumab; CEMIPL = cemiplimab; CrI = credible intervals; DURV = durvalumab; GEM = gemcitabine; HR = hazard ratios; i = induction; IPI = ipilimumab; Nab-PAC = nab-paclitaxel; NMA = network meta-analysis; NIVO = nivolumab; PAC = paclitaxel; PEM = pemetrexed; PEMBRO = pembrolizumab; PFS = progression-free survival; PLAT = platinum chemotherapy; RAM = ramucirumab; RE = random-effects; SEL = selpercatinib; SINT = sintilimab; TISL = tislelizumab

Figure 3.16: Network diagram for treatments included in the NMA for OS

Based on Figure 17, CS[3]
ATEZ = atezolizumab; BEV = bevacizumab; c =continuous; CAMR = camrelizumab; CEMIPL = cemiplimab; CrI = credible intervals; DURV = durvalumab; GEM = gemcitabine; HR = hazard ratios; i = induction; IPI = ipilimumab; Nab-PAC = nab-paclitaxel; NMA = network meta-analysis; NIVO = nivolumab; OS = overall survival; PAC = paclitaxel; PEM = pemetrexed; PEMBRO = pembrolizumab; PLAT = platinum chemotherapy; RAM = ramucirumab; RE = random-effects; SEL = selpercatinib; SINT = sintilimab; TISL = tislelizumab

Appendix D[8] described the methods of data imputation: for ORR, where n or N were missing, the other plus the proportion were used or the number randomised assumed for N. It was stated that if neither n or the proportion was reported then, if both complete response (CR) and partial response (PR) were reported, these were combined to attain the missing n. For survival, an HRs was required, which missing from only one study, RATIONALE 304, thus leading to the use of KM curves to reconstruct the IPD and thus estimate the HR.

3.4.2.2 NMA results

Overall, the results of the limited NMA suggested that selpercatinib is likely to lead to benefits in ORR, PFS and OS compared to both pemetrexed plus platinum-based chemotherapy and pembrolizumab combination therapy in RET fusion-positive patients with advanced NSCLC.

The results in each table below provide 1) the estimate for pemetrexed plus platinum chemotherapy versus selpercatinib derived from the propensity matching analysis, where the pemetrexed plus platinum chemotherapy arm data was derived from KEYNOTE-189 RCT, and 2) the estimate for pembrolizumab plus pemetrexed plus carboplatin/cisplatin versus selpercatinib, which was an indirect estimate based on a) the data for pembrolizumab plus pemetrexed plus carboplatin/cisplatin versus pemetrexed plus platinum chemotherapy, and b) the data for pemetrexed plus platinum chemotherapy versus selpercatinib derived from the propensity matching analysis. The effects for pembrolizumab plus

pemetrexed plus carboplatin/cisplatin versus pemetrexed plus platinum chemotherapy are not provided, as the intention is to provide only the results relating to selpercatinib. The results provided in the CS[3] are for the comparator versus selpercatinib. Therefore, the EAG has appended a column to provide the reciprocal result, which compares selpercatinib to the comparator (which would generally be regarded as the more standard approach for presentation of the results of a study drug relative to its comparators).

3.4.2.2.1 ORR

Both comparators had a significantly lower odds of an objective response than selpercatinib (Table 3.46).

Table 3.46: Relative treatment effect estimates expressed as pairwise ORs versus selpercatinib (with 95% CrI) for ORR, random effects model

Treatment	Pairwise OR (95% CrI) of comparators versus selpercatinib	Pairwise OR (95% CrI) of selpercatinib versus comparators
Pemetrexed plus platinum-based chemotherapy	[redacted]	[redacted]
Pembrolizumab plus pemetrexed plus carboplatin/cisplatin	[redacted]	[redacted]
Based on Adapted from Table 24, CS[3] CrI = credible interval; CS = company submission; OR = odds ratio; ORR = objective response rate		

3.4.2.2.2 PFS

Both comparators had a significantly higher hazard of disease progression than selpercatinib (Table 3.47).

Table 3.47: Relative treatment effect estimates expressed as HRs versus selpercatinib (with 95% CrI) for PFS, random effects model

Treatment	Median HR (95% CrI) of comparators versus selpercatinib	Median HR (95% CrI) of selpercatinib versus comparators
Pemetrexed plus platinum-based chemotherapy	[redacted]	[redacted]
Pembrolizumab plus pemetrexed plus carboplatin/cisplatin	[redacted]	[redacted]
Based on Adapted from Table 26, CS[3] CrI = credible interval; CS = company submission; HR = hazard ratio; ORR = objective response rate		

3.4.2.2.3 OS

Both comparators had a significantly higher hazard of death than selpercatinib (Table 3.48).

Table 3.48: Relative treatment effect estimates expressed as HRs versus selpercatinib (with 95% CrI) for overall survival (OS), random effects model

Treatment	Median HR (95% CrI) of comparators versus selpercatinib	Median HR (95% CrI) of selpercatinib versus comparators
Pemetrexed plus platinum-based chemotherapy	[redacted]	[redacted]

Treatment	Median HR (95% CrI) of comparators versus selpercatinib	Median HR (95% CrI) of selpercatinib versus comparators
Pembrolizumab plus pemetrexed plus carboplatin/cisplatin	[redacted]	[redacted]
Based on Adapted from Table 28, CS[3] CrI = credible interval; CS = company submission; HR = hazard ratio; OS = overall survival		

3.4.2.3 Meta-regression

Several key areas of heterogeneity were identified between trials included in the NMA including baseline characteristics, sex distribution and proportion of Asian patients. For example, some studies were conducted exclusively in older populations (65-Plus and LOGIK1201). In addition, some studies only reported data on populations of mixed histologies despite the NMA primarily reporting on non-squamous subgroup data in line with the population of interest in LIBRETTO-001.

To assess the impact of this between trial heterogeneity on the trial results, a meta-regression was performed to adjust for baseline characteristics between included studies. The meta-regression was restricted to studies with non-missing data and may be subject to limitations owing to the inclusion of potentially inaccurate data from studies with mixed histology data only. Various covariates including median age, sex, proportion of Asian patients and year of initial publication were included one at a time to assess whether they improved model fit. The analyses were performed for each endpoint (OR, OS and PFS). No baseline characteristics were identified as significant, suggesting the impact of any heterogeneity on the model results would be minimal.

3.4.2.4 Assessment of inconsistency

Inconsistency in the NMAs was assessed using the inconsistency versus consistency method, which compares the residual deviances between the two. Prior to commencing the approach, each pairwise treatment comparison predicted from the NMA was compared to the corresponding comparison in a trial. This helped to identify where inconsistencies may be present and which studies or treatment arms could be contributing to these.

The results of the inconsistency assessment are provided in Table 3.49 below. In all assessments the consistency of deviance information criterion (DIC) and residual deviance was similar (within the range of +/- 5 points) to the inconsistency of DIC and residual deviance. It is therefore concluded that no evidence of inconsistency was detected in the vast majority of analyses.

Table 3.49: Result of inconsistency assessment on the NMAs

Analysis	Consistency model		Inconsistency model		Number of data points
	Dbar	DIC	Dbar	DIC	
OS	26.58	48.22	27.90	51.57	31
PFS	26.38	48.16	26.97	50.81	28
ORR	45.69	86.76	43.28	85.76	51
Based on Table 29, CS[3] CS = company submission; Dbar = mean sum of residual deviances; DIC = deviance information criterion; NMA = network meta-analysis; ORR = overall response rate; OS = overall survival; PFS = progression-free survival					

EAG comment:

- The EAG considers that the NMA was conducted generally adequately. However, given the lack of justification for the choice of pemetrexed plus platinum chemotherapy and the KEYNOTE-189 trial, in the clarification letter, the EAG requested that NMA sensitivity analyses be conducted with different "pseudo-comparators" i.e., ITCs with different comparators in order to connect with the network, to which the company responded, "*As outlined in response to A21 above, and as mentioned in Section B.2.8.1 of the Company Submission, KEYNOTE-189 was the only trial to provide IPD and the pemetrexed plus platinum chemotherapy was used as a pseudo-comparison because Lilly only had permission to use IPD from this arm of the KEYNOTE-189 trial. As discussed in response to Question A23, imbalances in baseline characteristics caused by RET-fusion positive patients typically being younger and healthier than NSCLC patients as a whole means that population-adjusted methods such as a MAIC would reduce the available sample size and introduce uncertainty and potentially bias to the analyses. As such, an IPD method has been selected and the use of a population adjusted approach is not presented. As noted above, the lack of available IPD mean it is not possible to conduct an ITC with comparators other than pemetrexed plus platinum chemotherapy*." A detailed critique of the ITC and the use of KEYNOTE-189 can be found in Section 3.4.5.1.
- As mentioned in Section 2.3, the EAG does not accept that all comparators in the scope were included for the non-squamous population. Given the lack of reporting of results, in the clarification letter the EAG requested that for all outcomes for which a NMA was conducted (and for any further NMAs requested in A19), there should be a grid detailing the NMA treatment effect estimates (HRs and ORs) for all permutations of treatment comparisons involved in the network, as well as a ranking of all treatments involved in the network. The company responded by stating that, "*The NMA which analysed OS, PFS and ORR to provide relative treatment effect estimates of comparative efficacy between selpercatinib and comparators was conducted from a Global perspective to inform reimbursement activities across various geographies. As such, additional comparators that are not relevant to the UK setting were included. Given their lack of relevance to the current submission (see response to Question A9 for further detail), an updated network diagram for each outcome that includes these other treatment options has not been provided…. As discussed in response to Part a) of this question, this information is not provided given that Lilly do not consider these treatment options to represent relevant comparators in the current appraisal….. As discussed in response to Part a) of this question, this information is not provided given that Lilly do not consider these treatment options to represent relevant comparators in the current appraisal*." The EAG considers that the company's rationale for excluding other comparators is weak, based as it is upon clinical opinion. A better approach would have involved the inclusion of all feasible comparators in the NMA. This would have led to the same conclusion that selpercatinib is the best treatment, if the expert opinion that these comparators are inferior is true. However, NMAs and other rigorous methods of comparison exist for the very reason that expert opinion is often inaccurate. Therefore, if the clinical opinion that the comparators are inferior is false, then it is possible that a more inclusive NMA may have produced a result that contradicts the NMA result presented in the CS. Therefore, this is a key issue (see Section 2.3).
- As already stated in Section 3.3, all three studies, KEYNOTE-021, KEYNOTE-189 and KEYNOTE-189 Japan, that compared pembrolizumab plus pemetrexed plus platinum chemotherapy to pemetrexed plus platinum chemotherapy were included in the NMA to indirectly estimate the treatment effect of the former versus selpercatinib given that an ITC was used to estimate the treatment effect of the latter versus selpercatinib.[17, 18, 20] This means that any heterogeneity and trial selection for pooling will have implications for the comparison between

selpercatinib and the pembrolizumab combination. One source of heterogeneity that may exist between comparisons in the network is RET fusion-positive status. Information on RET fusion-positive status was not provided for those three trials. Since the vast majority (98%) of people with NSCLC are RET-fusion negative, a sample where RET-fusion status is not defined is highly likely to have a preponderance of RET fusion-negative participants. Therefore, it is probably that the three trials would possess mostly RET fusion-negative status. They would therefore be very different to LIBRETTO-001 SAS1, where all patients are RET fusion-positive. Such a difference in RET fusion status between comparisons will be a problem if RET fusion status has the capacity to affect outcome. As explained in Section 3.4.1.5, the company does not think that RET-fusion status is independently prognostic, because the effect of this variable on outcome became non-significant after adjustment for factors with which it was believed to correlate. However, although a lack of a true effect is one conclusion that can be drawn to explain the null effect, another possible cause is a lack of statistical power in the analysis. This is highly likely given the large ratio of covariates to sample size in the regression, in conjunction with the persistence of a point-estimate of clinically important magnitude. Given the possibility, therefore, that RET fusion-positive status is indeed a treatment effect modifier, the high likelihood that RET-positive status is different between these trials creates a concern about the validity of the NMA, a solution for which would be and RCT in the RET fusion-positive population (see Section 3.2.8).

- In Section 3.3, Tables 3.35 and 3.36 summarise the baseline characteristics of the LIBRETTO-001 study and the three studies used for comparison B. These tables do not demonstrate any clear clinical heterogeneity between the four studies (and thus comparisons A and B) for most variables, but there appear to be differences in the source of patients. The KEYNOTE-189 Japan study comprised participants who were all from Japan, whereas the other studies did not. Therefore, clinical heterogeneity may also have arisen from differing ethnicity/clinical practice, as well as differing RET fusion-status, which raises further concern regarding heterogeneity in the NMA.
- The company also did not present the outcomes separately for each of the three trials for the comparison of pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy. The EAG have therefore compiled these for OS and PFS in Table 3.50.
- The point estimates in Table 3.50 seem to indicate some heterogeneity of outcomes, the implications of which have not been explored directly in the CS i.e., by testing the effect of excluding any of the studies from pooling. This is therefore explored in Section 3.5.
- There is no evidence that an NMA or any kind of comparative analysis was performed for the outcome of AEs. This is a key issue as it prevents the Committee being able to properly weigh up the benefits against the potential harms of pembrolizumab.

Table 3.50: Relative treatment effect estimates expressed as HRs of pembrolizumab plus pemetrexed plus platinum chemotherapy versus. pemetrexed plus platinum chemotherapy

Trial	OS HR (95% CrI)	PFS HR (95% CrI)
KEYNOTE-189 (N=616)	0.49 (0.38,0.64)	0.52 (0.43,0.64)
KEYNOTE-189 Japan (N=40)	0.29 (0.07,1.15)	0.62 (0.27,1.42)
KEYNOTE-021 (N=123)	0.90 (0.42,1.91)	0.53 (0.31,0.91)

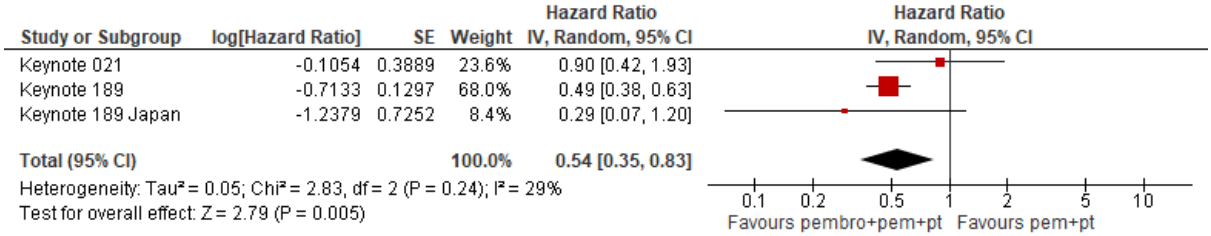
Based on Gandhi et al 2018, Langer et al 2016, Horinouchi et al 2021[17, 18, 20]
CrI = credible interval; HR = hazard ratios; OS = overall survival; PFS = progression-free survival

3.5 Additional work on clinical effectiveness undertaken by the EAG

The EAG performed a meta-analysis of the trials of pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy for the outcomes of OS and PFS.

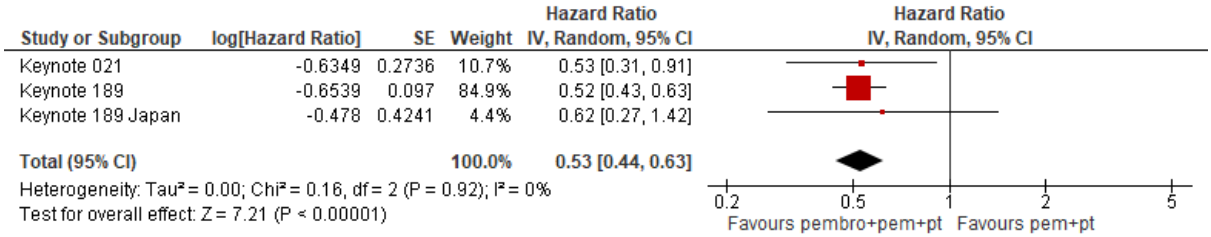
Statistical testing for heterogeneity yielded an I^2 of 29% for OS (Figure 3.17) and 0% for PFS (Figure 3.18). Therefore, most of the point estimate differences within each outcome could be argued to be explained by sampling error rather than the effects of any outcome modifiers. Nevertheless, given the likely differences in RET fusion status between studies, and the definite differences between studies in ethnicity, the possibility remains that the clear point estimate differences are at least partially driven by these covariates and that it is a lack of statistical power that prevents more significant I^2 values. Therefore, heterogeneity of trials in the NMA has been identified as a key issue.

Figure 3.17: Meta-analysis of the three trials comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for OS



CI = confidence interval; OS = overall survival; PEM = pemetrexed; PEMBRO = pembrolizumab; PT = platinum

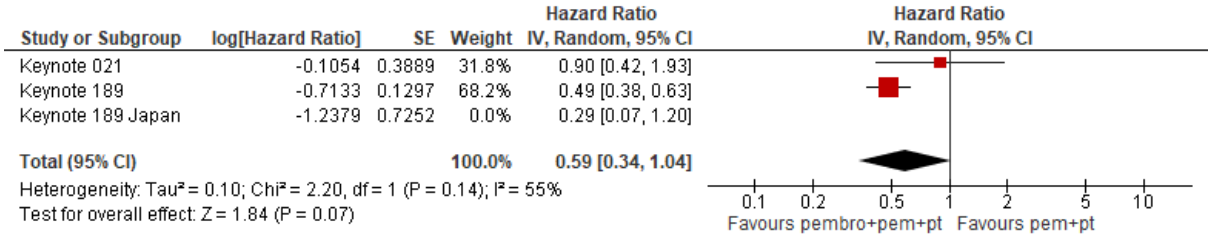
Figure 3.18: Meta-analysis of the three trials comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for PFS



CI = confidence interval; PEM = pemetrexed; PFS = progression-free survival; PEMBRO = pembrolizumab; PT = platinum

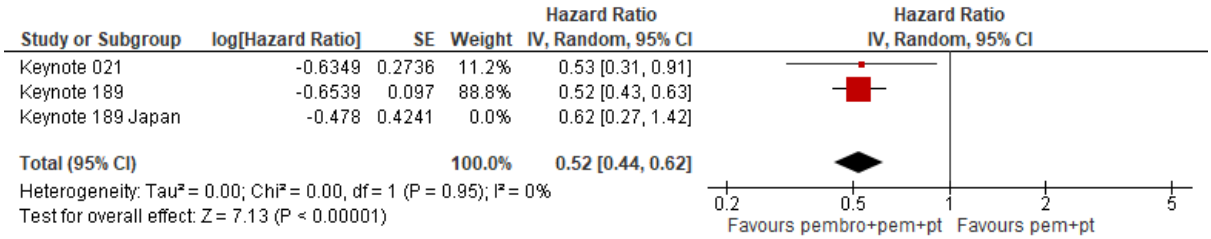
As a sensitivity analysis, the EAG removed the KEYNOTE-189 Japan study from the meta-analyses for both outcomes. The decision to remove this study was made for two reasons. Firstly, KEYNOTE-189 Japan was the greatest outlier for the main outcome of OS. Secondly, the EAG agreed that the most likely source of clinical heterogeneity within these three studies was ethnicity, because it was known that the KEYNOTE-189 Japan population were exclusively Japanese nationals, whereas the other two studies comprised <10% Asian participants. Therefore, given that clinical heterogeneity was most likely to result from different ethnicity in KEYNOTE-189 Japan, removing the KEYNOTE-189 Japan study was deemed the most likely way to reduce such heterogeneity. As Figure 3.19 shows, the removal of KEYNOTE-189 Japan reduced the magnitude of the OS effect from 0.54 to 0.59. Although this difference may not appear large, the EAG would prefer to see this revised estimate used in the NMA, as it may have an important knock-on effect on cost-effectiveness. Therefore, possible NMA heterogeneity is a key issue.

Figure 3.19: Meta-analysis of the three trials comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for OS, with the effects from KEYNOTE-189 Japan not included in the pooled result



CI = confidence interval; OS = overall survival; PEM = pemetrexed; PEMBRO = pembrolizumab; PT = platinum

Figure 3.20 Meta-analysis of the three trials comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for PFS, with the effects from KEYNOTE-189 Japan not included in the pooled result



CI = confidence interval; PEM = pemetrexed; PEMBRO = pembrolizumab; PFS = progression-free survival; PT = platinum

3.6 Conclusions of the clinical effectiveness section

The CrIs yielded by the ITC and the NMA suggested that selpercatinib was significantly more effective in terms of ORR, PFS and OS than pemetrexed plus platinum chemotherapy and pembrolizumab plus pemetrexed plus carboplatin/cisplatin respectively. In all cases the point estimates could be regarded as being of a clinically significant magnitude. However, the validity of these results is in question for several reasons.

Firstly, the methodology used for adjusting of the pseudo-comparator arm to resemble the selpercatinib trial more closely may not have been optimal. Of the adjustment methods explored, it appears that the default PSM method led to the most conservative results, which supports the use of this method. However, because the array of methods explored by the company were limited, it is possible that unexplored methods (such as addition of multivariate regression on the matched sample) may have yielded results that were less favourable to selpercatinib than those observed by the default PSM approach. Most crucially, important prognostic factors might have been omitted, including RET fusion status, which some observational data in the RET fusion-positive population shows might seriously underestimate the effectiveness of the pemetrexed containing comparators. Secondly, the validity of the NMA results partly depend upon the validity of the choice of data for the pseudo-comparator arm. The choice of using the pemetrexed plus platinum chemotherapy data from the KEYNOTE-189 RCT as the pseudo-comparator arm is stated as being due to relevant IPD not being available from any other sources, which the EAG consider to be not a convincing rationale. It is likely that had other sources of pemetrexed plus platinum chemotherapy data been used then very different overall NMA results might

have been yielded. Both of these problems are a direct result of using one-arm trial data for selpercatinib. Had the company waited until the results of the randomised LIBRETTO-431 trial are complete, then these two issues would have been avoided, and there would have been far less risk of selection bias.

Applicability of the results is also under question. The lack of data on the characteristics of the UK target population means that it cannot be assumed that the trial participants were comparable to the target population. Given the array of potential effect modifiers shown by the sub-group analyses, it is possible that effects observed in the trial would not be the same as those that would be observed in the target population. In addition, there are suggestions that the subsequent therapies used in the trial would differ from those use in UK clinical practice. Again, this could lead to trial results that are not applicable to the target population, as well as producing a bias in the treatment effect.

The limited array of comparators in the decision problem (two) may also have influenced interpretations. Had other comparators been present, as requested by the NICE scope, selpercatinib may not have emerged as the most effective treatment. In this context, the important question for consideration is whether the limited array of comparators makes clinical sense, given the population of the decision problem, which is RET fusion-positive non-squamous NSCLC in the context of NG122. Even if the two comparators are agreed to be the only options that fit with this population, a further question is whether the evidence can be applicable to the broader population that includes squamous histology.

Finally, the quality of AE data was seriously compromised by there being no specific AE data for the participants fitting the decision problem definition. It is possible that the pattern AEs in this smaller group would be different to those in the wider group that were analysed. It is also the case that no NMA or any form of comparative analysis was carried out for AEs, preventing a rigorous assessment of benefits and harms.

4. COST-EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

A systematic literature search was performed to identify cost-effectiveness studies (CS, Appendix G).[8] No searches were conducted to identify health-state utility values (HSUV), and cost and healthcare resource use studies.

4.1.1 Searches performed for cost-effectiveness section

The following paragraphs contain summaries and critiques of searches related to cost-effectiveness presented in the CS.[3, 8] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[10, 11] The CS was checked against the STA specification for company/sponsor submission of evidence.[12]

Appendix G of the CS reported the literature searches used to identify cost-effectiveness studies.[8] Searches were conducted in March 2019. The searches were not updated.

A summary of the resources searched is provided in Table 4.1.

Table 4.1: Resources searched for the cost-effectiveness literature review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
MEDLINE and MEDLINE in-Process & E-pubs ahead of print	Ovid	Not reported	04/03/2019
Embase	Ovid	1974-1 March 2019	04/03/2019
EconLit	Ovid	1886-21 February 2019	04/03/2019
Health Technology Assessment (HTA) Database	Centre for Reviews and Dissemination (CRD) interface	2016-2019	04/03/2019
National Health Service Economic Evaluation Database (NHS EED)	Centre for Reviews and Dissemination (CRD) interface		04/03/2019

EAG comment:

- The CS provided details of the literature searches for the EAG to appraise.[3, 8]
- Searches were conducted to identify cost-effectiveness analyses.
- The cost-effectiveness searches were conducted in March 2019. Update searches were not conducted, so the searches were more than 3 years out of date. An update of the searches immediately prior to submission to NICE would have been appropriate and could have identified potentially relevant records published since March 2019. In response to clarification, the company explained that *'Due to time and resource constraints, an update to this SLR could not be completed in time for submission. Lilly do not anticipate that an updated will significantly impact the current decision problem or cost-effectiveness assessment. In addition, the publication of recent NICE appraisals for selpercatinib in the second line (TA760) and pralsetinib (TA812) in a similar*

indication provides confidence that the most relevant information for economic modelling is already available.'[13]

- No searches were conducted to identify HSUVs, and cost and healthcare resource use studies.
- The CS explained that utility values were obtained from the LIBRETTO-001 trial, so '*it was not deemed necessary to extract quality of life data from the economic SLR*' (Appendix H.1).[8]
- The CS reported in Appendix I.1 that cost and healthcare resource use searches were not conducted because the values used in their model were *'based on previously accepted values from prior NICE appraisals in NSCLC and validated by UK clinical experts'*.[8]
- A good range of databases were searched. Full details of the database searches, including the database name, host platform, and date searched, were provided.
- Conference proceedings and HTA organisation websites were searched, but full details of these searches were not reported. Full details of the HTA organisation website searches and a list of conferences of interest were provided in the response to clarification.[13]
- The database search strategies were well structured. They included truncation, proximity operators, synonyms, and subject headings (MeSH and EMTREE).
- The search strategies were not well reported, and so were not reproducible. The main issue with the database search strategy reporting related to the Boolean operator AND being replaced by an ampersand. The EAG assumes that the searches were conducted correctly as the results of each search line, and the final total of records retrieved, were provided.
- There were no language or date limits for all but one of the database searches. The MEDLINE search strategy was limited by date to '2000-current'. The CS did not report why this date limit was included in the MEDLINE search.
- It would have been preferable for the database search strategies to be presented exactly as run, rather than copied into a tabular format, as Item 8 of the PRISMA-S reporting checklist recommends.[14] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[15]
- Study design search filters for cost-effectiveness were included. The search filters were not cited, as current practice recommends.[14]
- MeSH terms rather than EMTREE terms were incorrectly included in the Embase search strategy (Table 42).

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost-effectiveness studies, utilities and costs and resource use are presented in Table 4.2.

Table 4.2: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Adult patients (≥18 years) with advanced/metastatic EGFR mutation positive NSCLC	Patients with intermediate-stage NSCLC
Intervention	Approved or investigational novel pharmacological interventions evaluated as first-line therapy (monotherapy or	Surgery or radiotherapy only

	Inclusion criteria	Exclusion criteria
	combinations with any other treatments will be included)	
Comparator	Any intervention or BSC	No exclusions
Outcomes(s) 1 (Published economic evaluations)	No limit	No exclusions
Outcomes(s) 2 (HRQoL studies)	No SLR conducted for HRQoL	No SLR conducted for HRQoL
Outcomes(s) 3 (Cost/resource use studies)	No SLR conducted for cost/resource use	No SLR conducted for cost/resource use
Study design 1 (Cost-effectiveness analysis studies)	Cost-effectiveness analyses Cost-utility analyses Cost-consequence analyses Cost-benefit analyses Cost-minimisation analyses Budget impact models	Studies only reporting costs will be excluded
Study design 2 (HRQoL studies)	No SLR conducted for HRQoL	No SLR conducted for HRQoL
Study design 3 (Cost/resource use studies)	No SLR conducted for cost/resource use	No SLR conducted for cost/resource use

Source: Table 46, Appendices.[8]
BSC = best supportive care; EGFR = epidermal growth factor receptor; HRQoL = health-related quality of life; NSCLC = non-small-cell lung cancer; SLR =systematic literature review

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost-effectiveness studies.

4.1.3 Conclusions of the cost-effectiveness review

The CS provides an overview of the included cost-effectiveness studies, but no specific conclusion was formulated. No searches were conducted to identify utility and resource use and costs studies.

EAG comment: Eligibility criteria were suitable for the SLR performed and the review for cost-effectiveness studies was performed adequately. However, searches to identify utility and resource use and costs studies were not conducted.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with reference case
Perspective on costs	NHS and PSS	Consistent with reference case

Element of health technology assessment	Reference case	EAG comment on company's submission
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with reference case
Synthesis of evidence on health effects	Based on systematic review	Not consistent with reference case (no review used to identify HRQoL studies)
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Consistent with reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Consistent with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Unclear whether the UK tariff was used
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Consistent with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with reference case

EAG = Evidence Assessment Group; EQ-5D = European Quality of Life-5 Dimensions; NHS = National Health Service; HRQoL = health-related quality of life; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALYs = quality-adjusted life years; UK = United Kingdom

4.2.2 Model structure

In line with a number of prior NICE appraisals in NSCLC (TA760, TA705 and TA683)[7, 21, 42], a cohort partitioned survival model (PSM) was developed including three mutually exclusive health states: a progression-free state, a progressed disease state, and death:

- Progression-free: Patients' disease is in a stable or responding state and not actively progressing. Patients in this state are assumed to incur costs associated with treatment acquisition, administration, treatment monitoring, medical management of the condition and the management of Grade 3/4 AEs. Patients also experience a higher utility compared with progressed disease.
- Progressed: Patients have met the RECIST v1.1 criteria for disease progression. Patients in this state may continue their allocated therapy for a time and/or have subsequent anti-cancer therapy

and incur costs associated with treatment acquisition, administration, medical management of the condition and terminal care. Patients experience a lower utility compared with progression-free disease

- Dead: Patients no longer incur costs, life years or utilities.

Patients were modelled to enter the model in the progression-free health state. Cumulative survival probabilities from PFS and OS parametric survival functions were then used to determine the proportion of patients in each heath state at each model cycle. The model was developed in Microsoft Excel.

A lifetime horizon (i.e., 25 years) with a cycle length of 1 week was applied to ensure all costs and QALYs were captured.

EAG comment: The main concern of the EAG relates to the use of a partitioned survival model without exploring a state transition model (STM) approach alongside it. The NICE DSU TSD19 recommended the use of STMs alongside PSMs to verify the plausibility of PSM extrapolations and to explore key clinical uncertainties in the extrapolation period. This was not done by the company, and the EAG was concerned that the chosen PSM may not be fully validated. In response to clarification question B1, the company acknowledged that a PSM approach assumes that the modelled survival endpoints are structurally independent and that this may represent a limitation of the selected approach. The company further acknowledged that the PSM approach may over- or under-estimate long-term outcomes if the HR calculated from the observed period does not accurately reflect the expected HR in the extrapolated period. Nevertheless, the company argued that PSM and STM estimates typically converge as the data mature and prior NICE appraisals of oncology treatments indicated that the choice of a PSM or STM approach typically has a limited impact. However, PFS and OS data for selpercatinib from LIBRETTO-001 were relatively immature at the June 2021 data cut-off (42% had progressed and [redacted] had died), and the large majority of (PF)LY gains were accumulated beyond the observed data period. Hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted (as requested but not provided in the company's response to clarification question B23). To assist in verifying the plausibility of the PSM extrapolations, the EAG would like to see the outcomes of a STM.

4.2.3 Population

The population considered in the CS was treatment-naïve patients with advanced non-squamous RET fusion-positive NSCLC who require systemic therapy, which is narrower than the population defined in the final NICE scope.

The modelled baseline patient characteristics were presented in Table 38 of the CS. These were based on the baseline characteristics of patients who received selpercatinib in the LIBRETTO-001 trial and were considered representative of patients in UK clinical practice.

The key baseline patient characteristics in the economic model are listed in Table 4.4 below.

Table 4.4: Key baseline patient characteristics used in the economic model

Model parameter	Value	Source
Mean age (years)	[redacted]	LIBRETTO-001 (SAS1)
Female (%)	62.3	LIBRETTO-001 (SAS1)
Mean weight (kg)	[redacted]	LIBRETTO-001 (SAS1)
Based on CS Table 38 CS = company submission		

EAG comment: The main concern of the EAG relates to the modelled population being narrower than the population defined in the NICE scope. Although the population defined in the NICE scope is *adults with untreated advanced RET fusion-positive non-small cell lung cancer (NSCLC)*, the company stated in Table 1 of the CS that the evidence presented in the submission is for patients with non-squamous histology. In response to the clarification letter, the company stated that, whilst squamous histology was not an exclusion criterion for enrolment in the LIBRETTO-001 trial, owing to the rarity of RET fusion-positive squamous histology, no squamous patients were enrolled into the SAS1 population. In addition, the company argued that clinical experts were expected to follow the same recommendation for people with squamous advanced NSCLC as for people with non-squamous advanced NSCLC. Notwithstanding the advice from clinical experts, the EAG does not think it is ideal that recommendations are applied to populations other than those on whom selpercatinib has been trialled. More details regarding this issue are provided in Section 2.1

4.2.4 Interventions and comparators

The intervention considered in the CS was selpercatinib. In line with the existing licensed dose in advanced pre-treated RET fusion-positive NSCLC, selpercatinib (160 mg) was administered orally twice daily in 28-day cycles until PD or unacceptable toxicity, or any other reasons for treatment discontinuation.

The comparators considered were pembrolizumab combination therapy (pembrolizumab [200 mg] plus pemetrexed [500 mg/m^2] plus platinum chemotherapy [carboplatin AUC 5 mg/ml x min]) and pemetrexed (500 mg/m^2) plus platinum chemotherapy (carboplatin AUC 5 mg/mL x min). Pembrolizumab was given in 21-day cycles up to 2 years or until disease progression, carboplatin was given up to 4 x 21-day cycles (6 x 21-day cycles in the pemetrexed plus platinum chemotherapy arm) or until disease progression, and pemetrexed was given up to disease progression.

Several comparators listed in the NICE scope (described in Table 1 of the CS) were not considered in the current submission. The company stated that, as the target population has been restricted to patients with non-squamous histology, comparators relevant to the squamous population were not included in the submission. Pralsetinib was not considered a relevant comparator in this population as it has not received a positive recommendation from NICE, and therefore was not considered part of routine practice. In addition, the company argued that patients with a positive RET status are most commonly treated with either pemetrexed with platinum-based chemotherapy or pembrolizumab plus pemetrexed with platinum-based chemotherapy, and as such, these were the only comparators considered relevant to this submission.

EAG comment: The main concern of the EAG relates to comparators listed in the NICE scope that were not considered in the current submission. Pembrolizumab monotherapy, atezolizumab monotherapy, atezolizumab plus bevacizumab, carboplatin and paclitaxel and platinum doublet chemotherapy with or without pemetrexed maintenance treatment were not included as comparators, although they were all included in the scope, as well as the NG122 care pathway. In response to the clarification letter, the company stated that comparator choice was informed by feedback received from expert oncologists practicing in the NHS and supported by an RWE study to ensure only the most relevant comparators to selpercatinib in UK clinical practice were selected. The EAG also asked the company to conduct all effectiveness analyses, whether by ITC or NMA or combination (as in the CS), and cost-effectiveness analyses including all comparators in the scope and the NG122 care pathway. The company did not provide any of these. The EAG was not satisfied with the company's response

and concluded that the company rejected NICE-recommended comparators based on clinical opinion and an arbitrary selection of evidence. More details regarding this issue are provided in Section 2.3.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and PSS perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 1 week with a lifetime time horizon (25 years).

EAG comment: The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main source of evidence on treatment effectiveness used for selpercatinib is the single-arm LIBRETTO-001 study. The SAS1 analysis set of this study was used to populate the model. The company considered this to be representative of patients in UK clinical practice.

A propensity score matching approach based on the KEYNOTE-189 study was used to compare selpercatinib with a matched reference arm for pemetrexed plus platinum chemotherapy. The pembrolizumab combination therapy was modelled through the application of a HR to the pemetrexed plus platinum chemotherapy reference arm extrapolation that was generated through an NMA.

The main outcomes for treatment effectiveness were PFS and OS. The company stated that the criteria considered for determining the best parametric fit were: 1) goodness-of-fit statistics (AIC and BIC); 2) assessment of visual fit to the observed KM curve; and 3) clinical expert opinion regarding the plausibility of the long-term extrapolations of each function.

4.2.6.1 Company's base-case parametric curves for PFS, OS and TTD

4.2.6.1.1 PFS

To estimate long-term PFS for selpercatinib and comparators, PFS data generated for selpercatinib, and the matched reference arm (pemetrexed plus platinum chemotherapy) were extrapolated through applying parametric survival functions. Progression-free survival for pembrolizumab combination therapy was then constructed through applying a HR as generated through the NMA.

As part of the survival analyses for PFS, the following parametric functions were explored:

- Unstratified (with treatment as an indicator variable) exponential, Weibull, Gompertz, lognormal, loglogistic, generalised gamma and gamma.
- Stratified Weibull, Gompertz, lognormal, loglogistic, generalised gamma and gamma.
- Stratified and unstratified spline models (with one, two, and three knots).

The company argued that because of the short duration of follow-up all curves had a similar visual and statistical fit (as measured by Akaike information criterion (AIC) and Bayesian information criterion (BIC)), and hence argued that it was not possible to specify an optimal curve choice based on visual and statistical fit. Therefore, clinical feedback from UK-based expert oncologists on the long-term validity of the survival curves was sought. In addition, the company cited a physician stating that the effectiveness of selpercatinib in RET fusion-positive patients was comparable to those of ALK-positive patients treated with targeted therapies. Based on feedback from UK-based expert oncologists and the comparison with ALK-positive patients treated with targeted therapies, the Gompertz curve was selected to model PFS for selpercatinib and pemetrexed plus platinum-based chemotherapy. Progression-free survival for the pembrolizumab combination therapy arm was modelled by applying

the HR (0.517 [0.401, 0.681]) from the NMA to the pemetrexed plus platinum-based chemotherapy arm.

4.2.6.1.2 OS

To estimate long-term OS for selpercatinib and comparators, OS data generated for selpercatinib, and the matched reference arm (pemetrexed plus platinum chemotherapy) were extrapolated through applying parametric survival functions. The OS for pembrolizumab combination therapy was then constructed through applying a HR as generated through the NMA.

As part of the survival analyses for PFS and OS, the following parametric functions were explored:

- Unstratified (with treatment as an indicator variable) exponential, Weibull, Gompertz, lognormal, loglogistic, generalised gamma and gamma.
- Stratified Weibull, Gompertz, lognormal, loglogistic, generalised gamma and gamma.
- Spline models (with one, two, and three knots).

In line with PFS, the company argued that it was not possible to select the optimal curve based on visual or the statistical fit and clinical feedback was sought. Based on clinical expert opinion, the company selected the spline knot 1 model for the modelling of OS in the selpercatinib and pemetrexed plus platinum-based chemotherapy arms. The HR from the NMA (0.610 [0.489, 0.761]) was then applied to the pemetrexed plus platinum-based chemotherapy arm to model OS for the pembrolizumab combination arm.

4.2.6.1.3 TTD

To estimate the duration of treatment for selpercatinib, TTD was modelled in line with the approach taken for PFS and OS. Time to treatment discontinuation for the comparators was modelled using the selpercatinib PFS curve for the intervention, capped at a maximum number of cycles (where specified in the SmPC). The company considered this to be a conservative approach.

For the modelling of selpercatinib TTD, an exponential curve was selected in the company's base-case. The company argued that the exponential curve was the best fitting curve (based on AIC and BIC) and was deemed clinically plausible due to it lying above the PFS landmark estimates, in line with feedback from clinical expert oncologists which suggested treatment would continue for a short period post-progression. Table 4.5 reports further detail regarding the criteria for the choice of survival curves for PFS, OS and TTD.

Table 4.5: Criteria for the choice of survival curves

	PFS	OS	TTD
General considerations	**Pemetrexed plus platinum chemotherapy** Modelled by applying the same parametric curve as for selpercatinib. **Pembrolizumab combination therapy** Modelled by applying the HR resulting from the NMA.	**Pemetrexed plus platinum chemotherapy** Modelled by applying the same parametric curve as for selpercatinib. **Pembrolizumab combination therapy** Modelled by applying the HR resulting from the NMA.	**Pemetrexed plus platinum chemotherapy** TTD was modelled using PFS. **Pembrolizumab combination therapy** TTD was modelled using PFS.
Statistical fit to the observed data (based on AIC and BIC)	**Selpercatinib** The AIC indicates that the split knot 3 curve has the best statistical fit. The BIC indicates that the log-logistic curve has the best statistical fit.	**Selpercatinib** AIC and BIC indicate that the log-normal curve has the best statistical fit.	**Selpercatinib** AIC and BIC indicate that the exponential curve has the best statistical fit.
Visual fit to the observed data	The company considered all curves to have a similar visual fit in the selpercatinib and pemetrexed plus platinum-based chemotherapy arms.	The company considered all curves to have a similar visual fit in the selpercatinib and pemetrexed plus platinum-based chemotherapy arms.	The company considered all curves to have a similar visual fit in the selpercatinib arm.
Fit to observed data (from the LIBRETTO-001 trial)	The loglogistic and lognormal curve was excluded as selpercatinib PFS remained unrealistically high ([redacted] and [redacted] after 20 years). The spline knot 3 curve was excluded as PFS started to increase again.	Not discussed by the company	**Selpercatinib** The mean TTD after PFS was [redacted].
Clinical plausibility of the extrapolation (based on comparison with historical data)	One clinical expert stated that selpercatinib estimates in *RET* fusion-positive patients could be deemed comparable to those of *ALK*-positive patients treated with targeted therapies. Median PFS for two such therapies were found to be 24.02 months (brigatinib) and 34.8 months.[43, 44] All parametric curves resulted in a median survival between 23 and 27 months.	Tan *et al.* reports a median OS (49.3 months) for *RET* fusion-positive NSCLC patients treat with selective *RET* tyrosine kinase inhibitor.[45] The stratified lognormal curve (median survival 49.94 months) results in the lowest difference to results of this study Another study reported a median OS for the *ALK-1* inhibitor alectinib (48.2 months). The lognormal curve and the spline knot 1 curve (median survival 48.33 months) result in the lowest difference to the results of this study.	Not discussed by the company.
Clinical plausibility of the extrapolation (based on clinical expert opinion)	**Selpercatinib** The median PFS of the log-normal curve was closest to that produced by expert opinion (21 months).	**Selpercatinib** The median OS of the exponential curve [redacted] was closest to the mean (61 months) based on expert opinion.	**Selpercatinib** Experts stated that patients who progress often remain on treatment until they have

	PFS	OS	TTD
	Pemetrexed plus platinum chemotherapy The median PFS of the spline knot 3 curve [redacted] was closest to the mean based on expert opinion (6–11 months). None of the curves resulted in PFS values that were in the range specified by experts. **Pembrolizumab combination therapy** The median PFS of the exponential and the Gompertz curves [redacted] was closest to the mean (10.5 months) based on expert opinion (10-11 months). None of the curves resulted in PFS values that were in the range specified by experts.	**Pemetrexed plus platinum chemotherapy** The median OS of the spline knot 2 and stratified Gompertz curves was 12.2 months while the mean of the exponential and unstratified Gompertz curves was 12.43 months. The OS of these four curves fall into the range of expected OS based on expert opinion (12-24 months). **Pembrolizumab combination therapy** All curves resulted in OS values that were in the range specified by experts (12-24 months).	received a further two scans, with approximately 3 months between each scan.
Base-case approach	Unstratified Gompertz	(Unstratified) spline knot 1	Unstratified Exponential

AIC = Akaike information criterion; ALK = anaplastic lymphoma kinase; BIC = Bayesian information criterion; HR = hazard ratio; NMA = network meta-analysis; NSCLC = non-small-cell lung cancer; OS = overall survival; PFS = progression-free survival; RET = rearranged during transfection; TTD = time to treatment discontinuation

EAG comment: The main concerns of the EAG relate to: a) immaturity of the LIBRETTO-001 survival data; b) survival curve choice transparency; c) no treatment waning; d) underestimation of the comparator PFS compared to the LIBRETTO-001 trial; e) substantial differences between modelled TTD and observed median TTD after progression and f) substantial differences of comparator PFS compared to alternative sources.

a) Data from the LIBRETTO-001 trial for the modelling of PFS and OS for selpercatinib were relatively immature (42% had progressed and [redacted] had died), adding substantial uncertainty to the extrapolated survival data in the economic model. In addition to the company's scenario analyses in the CS, the EAG conducted scenario analyses to explore a range of plausible PFS and OS curves. Plausibility was based on 1) the curve being closer to an expert estimate or external data than the curve chosen by the company, and 2) the curve having a plausible shape. Scenario analyses for the comparison with pembrolizumab combination therapy resulted in the net monetary benefit (NMB) ranging between £39,808 (Gompertz for PFS and stratified Gompertz for OS) and £67.101 (exponential curves for PFS and OS). Scenario analyses (conditional on the EAG base-case) for the comparison with pembrolizumab combination therapy resulted in the NMB ranging between £39,808 (Gompertz for PFS and stratified Gompertz for OS) and £67,101 (exponential curves for PFS and OS). Scenario analyses for the comparison with pemetrexed plus platinum chemotherapy resulted in the NMBs ranging between -£36,197 (Gompertz for PFS and stratified Gompertz for OS) and -£8,192 (exponential for PFS and OS). The EAG's scenario analyses resulted in a wide range of NMBs, which confirms the substantial uncertainty surrounding the extrapolated survival data.
b) The EAG considered the company's choice of survival curves for the modelling of treatment effectiveness in the health economic model not transparent: The EAG considered the company's choice of survival curves for the modelling of treatment effectiveness in the health economic model not transparent:
    a. Next to the standard parametric models, the company also considered complex parametric survival curves (i.e., spline models) for the modelling of PFS and OS and implemented the spline knot 1 model for the modelling of OS in its base-case. The NICE DSU TSD 21 guidance states that more complex survival curves should be considered when hazard functions are observed, or expected in the longer-term, to have complex shapes (i.e., where there are two or more turning points, or where there are two or more important changes in the hazard function slope). However, based on the presented evidence, it was unclear to the EAG why the company selected a spline model for the modelling of OS rather than a standard parametric model. Upon request for clarification, the company argued that complex curves were added 'in the interest of maximising clinical plausibility', which, according to the EAG, does not justify why standard parametric curves were insufficient for the modelling of OS.
    b. To examine the diagnostics of the parametric survival models based on the observed data, the EAG requested plots for standard normal quartiles versus log time and log survival odds versus log time. The company did not provide these plots, stating that they were not available.
    c. Due to the immaturity of data, the company considered the visual and statistical fit of parametric survival curves to the KM data an insufficient basis for the selection of the most appropriate survival curves. Expert opinion was therefore sought to inform the choice of survival curves. However, Table 4.5 highlights that the company's selected survival curves were not always those closest to the expert inputs. For example, the company modelled PFS using an unstratified Gompertz curve, but the median survival

resulting from this curve was not closest to the expert inputs for selpercatinib or pemetrexed plus platinum chemotherapy. It was not clear to the EAG why the company did not select the curves that were closest to the expert inputs.

d. The modelled PFS and OS values as reported in CS, Tables 41 and 44 do not match with the values informing PFS and OS in the economic model for several survival curves, including the company's base-case. The EAG was unable to identify the source of this mismatch and the potential impact on the cost-effectiveness results is unclear. This mismatch and the opacity relating to its source add to the lack of transparency in the choice of survival curves.

The non-transparent survival model selection, in addition to the immaturity of the LIBRETTO-001 trial data, adds substantial uncertainty to the extrapolated PFS, OS, and TTD data. As highlighted in the scenario analyses described in EAG comment a) and Section 6.1.2, the range of NMBs varies by up to £28.000.

c) The company assumed that there was no waning of the selpercatinib treatment effect in its base-case. Rationale was provided in CS, Table 36, suggesting that the selected OS and PFS parametric survival curves were validated by UK clinical experts on the most clinically plausible long-term efficacy estimates. In clarification question B10a the EAG requested further justification as to why no treatment waning was considered. The EAG also requested HR plots for PFS and OS versus time for both comparisons, as well as an updated economic model and scenario analyses exploring treatment waning kicking in at different time points. The company highlighted that there was no evidence of relative treatment waning in the single-arm LIBRETTO-001 trial for selpercatinib. In addition, the company argued that different assumptions on the long-term treatment effect would have been implicitly captured in the selected survival curves, that patients with RET fusion-positive advanced NSCLC have a poor prognosis, and that selpercatinib is a continuous, treat to progression treatment. Although plots of the smoothed hazard rates per arm were provided in response to the clarification letter, the company did not provide HR plots and did not provide scenario analyses exploring treatment waning in an updated economic model. The EAG would like to stress that these analyses are important for the assessment of the potential impact of treatment waning on the cost-effectiveness results, especially given that the current PFS and OS data are immature.

d) Based on the company's response to clarification question B23, the EAG noticed that the observed PFS for pemetrexed plus platinum chemotherapy (based on the 1.0 year or 1.5 years truncation points) is larger than the modelled PFS based on a lifetime time horizon. This suggests that the modelled PFS for pemetrexed plus platinum chemotherapy is underestimated and hence, the PFS increments for selpercatinib versus pemetrexed plus platinum chemotherapy are potentially overestimated in favour of the intervention.

e) In its base-case the company selected their optimal curve for the modelling of TTD based on its statistical and visual fit to the KM data, arguing that this was appropriate given the maturity of TTD data. The company selected the exponential curve, which resulted in a median TTD of [redacted] compared to a median modelled PFS of [redacted] months. This is not in line with clinical experts' inputs, which stated that patients are usually treated until approximately 3 months after progression. This was confirmed by the mean post progression TTD in the LIBRETTO-001 trial, which was [redacted]. The EAG therefore requested a scenario analysis in which TTD would be more in line with clinical experts' expert inputs and the post progression TTD in the LIBRETTO-001 trial. The company provided this analysis which decreased, the NMB by approximately £2,000, in each comparison.

f) Based on the company's PSM approach, median PFS for patients treated with pemetrexed plus platinum chemotherapy was approximately [redacted] months. The EAG, however, identified a

retrospective review of records that reports a median PFS of 19 months for patients with RET-rearranged lung cancers which were treated with pemetrexed-based therapies (like both comparators)[41]. The EAG, however, identified a retrospective review of records that reports a median PFS of 19 months for patients with RET-rearranged lung cancers which were treated with pemetrexed-based therapies (as with both comparators). Based on this evidence, the EAG considers the modelled effectiveness of pemetrexed plus platinum chemotherapy to be potentially underestimated, and hence the treatment effect of selpercatinib versus pemetrexed plus platinum chemotherapy overestimated.

4.2.7 Adverse events

The main sources of evidence used to inform AEs incidence rates were the LIBRETTO-001 trial for selpercatinib and the KEYNOTE-189 trial for the comparators.[3] The economic model included all Grade 3-4 AEs with at least 2% difference in reported frequency in the source trials between interventions (CS, Table 49). The consequences of AEs were modelled in terms of costs and utility decrements.

EAG comment: The main concerns of the EAG relate to: a) the approach of including AEs with at least a 2% difference in frequency between interventions in the included trials, b) mismatches between values related to AEs in the CS and the economic model, c) lack of justification on zero disutility and/or costs assumptions.

a) According to the CS, the company modelled all Grade 3-4 AEs with at least a 2% difference in frequency between the interventions in the included trials, rather than the more common approach of including grade ≥3AEs that occur in at least 2% or 5% in either arm. The company's current approach implies that AEs with a high incidence in both arms (e.g., 80% and 81%) would not be included in the modelling. Although this approach lacks face-validity and may add uncertainty to the cost-effectiveness results, the EAG acknowledges that applying a different approach as a one-off cost and disutility likely has a limited impact. Nonetheless, a per cycle analysis (rather than assuming a one-off cost and disutility) including all Grade 3-4 AEs that occur in at least 2% of any arm would be reassuring to the EAG.
b) The EAG identified several inconsistencies between values related to AEs reported in the CS and the economic model. In the economic model a zero disutility and/or duration was assumed for several AEs while different values were reported in CS, Table 51. Likewise, for the costs of several AEs there was a mismatch between the values reported in CS, Table 64 and the economic model (i.e., costs were assumed to be zero in the economic model, contrary to the costs reported in CS, Table 64). In addition, not all AEs reported in CS, Table 49 were also present in CS, Tables 51 and 64. The EAG would like the company to further justify these inconsistencies and provide a correct economic model if deemed appropriate.
c) Tables 51 and 64 from the CS reported the AEs disutilities and costs applied in the economic model. However, the company did not provide sufficient justification for some of the values used, despite being asked in the clarification letter. More specifically, several AEs were assumed to have a zero disutility without appropriate justification, and for several AEs the duration and/or utility decrement were reported without justification or reference to their source. The lack of justification is especially concerning for AEs (e.g., thrombocytopenia) which had a non-negligible incidence according to the trials In response to the EAGs request to provide justifications for the AE disutility and costs assumptions in clarification question B14,[13] the company acknowledged the *"potentially arbitrary assumption within the model"* and mentioned that the same approach was applied in other TAs. Although the EAG

understands that economic modelling is inherent to making assumptions, these should be supported by evidence, either from relevant external data or expert opinion and hence the company should provide this.

4.2.8 Health-related quality of life (HRQoL)

Health state utility values were estimated for the progression-free and progressed health states. Selpercatinib HRQoL data were collected in the LIBRETTO-001 trial using the EORTC QLQ-C30 questionnaire. These were completed by patients prior to receiving the drug on the first day of the treatment, every second cycle in the first year, every third cycle from cycle 13, and at the post-discontinuation follow-up visit. Due to the lack of EQ-5D data from the LIBRETTO-001 study, the company explored various mapping techniques to map the collected EORTC QLQ-C30 data to EQ-5D-3L (CS, Table 50). The CS base-case implemented the EQ-5D-3L results from the algorithm outlined by Young et al 2015,[46] as it resulted in the lowest, and according to the company most plausible utility estimates (CS, Table 50).

As per the CS, most responses to treatment with selpercatinib reported in the LIBRETTO-001 trial were partial responses. The company assumed that it was unlikely that responders would have an important improvement in their HRQoL, and hence an adjustment to the progression-free utility weight to reflect response was not deemed necessary.

4.2.8.1 Health-related quality of life data identified in the review

According to the CS, Appendix H,[8] QoL data was not deemed necessary to be extracted from the economic SLR, as the utility values for the selpercatinib model were obtained from the LIBRETTO-001 trial and mapped to EQ-5D data using the algorithm presented in Young et al 2015.[46]

4.2.8.2 Health state utility values

A summary of all HSUVs used in the cost-effectiveness analysis is provided in Table 4.6. For the CS base-case, utility values were assumed to be treatment independent. Scenario analyses were performed to explore utility values from other relevant TAs (i.e., TA654 and TA812).

Table 4.6: Health state utility values

	Health state	Utility value	Reference
CS base-case	PF	[redacted]	LIBRETTO-001 mapped with Young et al 2015 algorithm
	PD	[redacted]	
CS scenario analysis	PF	[redacted]	TA654[47]
	PD	[redacted]	

Based on CS, Tables 52 and 53
CS = company submission; PD = progressive disease; PF = progression-free

4.2.8.3 Disutility values

Disutility values were applied to the AE incidence rates from the LIBRETTO-001 and KEYNOTE-189 trials (CS, Table 49) to capture the impact of AEs on HRQoL in the economic model. All AEs were assumed to occur in the first cycle of the model and last for a prespecified duration (CS, Table 51). Each AE had a specific utility decrement based on previous NICE TAs and company's assumptions.

EAG comment: The main concerns of the EAG relate to: a) high utility values compared with other TAs, and small decrement between PF and PD utility values, b) use of mapping algorithm.

a) Utility values to inform the company's base-case (PF = [redacted], PD = [redacted]) were higher than the ones used in other relevant TAs, and only slightly lower than the age and gender matched UK general population norm (0.819). Moreover, the decrement for disease progression ([redacted]) seems relatively small. The company justified the high utility values and small progressed disease utility decrement with the fact that patients in the SAS1 population of the LIBRETTO-001 were younger than patients in other NSCLC TAs and were mainly non-smokers. Upon request, the company provided scenario analyses exploring utility values from other relevant TAs, resulted in higher ICERs (NMB not reported) ranging from £5,299 and £6,253 per QALY gained (original £5,264 per QALY gained) compared to pembrolizumab combination therapy and £36,046 to £41,985 per QALY gained (original £35,883 per QALY gained) compared to pemetrexed plus platinum chemotherapy. In response to clarification question B17b,[13] the company acknowledged that the number of completed post-progression HRQoL questionnaires was limited ([redacted] observations) and that this could potentially explain the relatively small utility decrement for progressed disease. The EAG agrees that the few HRQoL data informing PD utility were collected early after patients progressed and therefore may not capture the full impact of disease progression on HRQoL, which may have led to an overestimation of the PD utility. Therefore, the EAG preferred to inform their base-case using the PD utility (0.678) from TA654 (also accepted in TA812 for untreated patients with RET fusion-positive NSCLC), which resulted in ICERs of £5,599 and £42,187 per QALY gained when compared to pembrolizumab combination therapy and pemetrexed + platinum chemotherapy, respectively. Additionally, the EAG explored a scenario analysis with both PF (0.794) and PD utility values from TA654, which resulted in ICERs of £5,626 and £42,407 per QALY gained when compared to pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy, respectively.[47]
b) The company mapped EORTC QLQ-C30 data to EQ-5D data to inform HSUVs, because EQ-5D data were not collected in the LIBRETTO-001 trial. After comparing four different mapping techniques the company chose the mapping algorithm outlined by Young et al 2015,[46] as it had the lowest, and supposedly most plausible estimates. As per NICE TSD 10[48], when EQ-5D instruments may not be available, a mapping function can be used, as long as it has been demonstrated and validated. Given the number of mapping algorithms available and the fact the Young et al 2015 algorithm was based on a population that included patients with multiple myeloma (n=572), breast cancer (n=100) and lung cancer (n=99)[46], the EAG would have expected further justification based on literature on the validity of the specific mapping algorithm for this population of NSCLC.

4.2.9 Resources and costs

The cost categories included in the model were drug acquisition costs, medical costs (treatment administration and monitoring, subsequent treatments, medical management of the condition by health state), costs of managing AEs, and end of life costs.

Unit prices were based on the NHS reference prices, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF), Eli Lilly and Company, electronic market information tool (eMIT), and past relevant NICE TAs.

4.2.9.1 Resource use and costs data identified in the review

According to the CS, modelled costs and resource use were based on the targeted literature review of relevant and previously accepted TAs by NICE for first line treatments in patients with advanced and/or metastatic NSCLC. Therefore, no further extraction of studies from the SLR to identify cost-effectiveness studies was performed.

4.2.9.2 Treatment costs

Drug acquisition costs of selpercatinib were provided by the company, while the costs for relevant comparators were based on their list price extracted from the BNF or eMIT as summarised in Table 4.7.

Drug acquisition costs were divided into treatment periods according to the dosing schedules of each treatment as summarised in Table 4.8. Costs for treatment cycle 1 were based on the planned dosing schedule, while in the subsequent treatment cycles costs were adjusted to reflect the mean dose intensity observed in the trials. For selpercatinib, treatment costs in the first 4 weeks (period 1, 28 days) with a mean dose of 293.33 mg and a price of [redacted] per mg was [redacted] (including PAS). Thereafter (period 2, week 4+), the treatment costs per cycle with a mean dose of 251.07 mg and a price [redacted] per mg was [redacted] (including PAS). For the pembrolizumab combination therapy arm, the cost was £6,449.76 for period 1 (weeks 0-2), £5,507.45 for period 2 (weeks 3-11), £5,491.98 for period 3 (week 12-103), and £994.68 for period 4 (week 104+). Treatment costs of pemetrexed plus platinum chemotherapy were £1,189.76 for period 1 (week 0-2), £1,010.15 for period (week 3-17), and £994.68 for period 3 (week 18+).

A mean body weight of 72.2 kg and a body surface area of 1.81 m^2 were used for adjusted dose interventions as sourced from TA520[49]. The weighted average cost was applied in the model for selpercatinib to account for dose reductions for toxicity control and weight-based dosing. A relative dose intensity (RDI) equivalent to selpercatinib from LIBRETTO-001 was applied to the comparators.

Drug wastage was also applied in the company's base case, assuming a whole tablet for oral drugs and the lowest cost of opened vials for the available sizes.

Table 4.7: Drug acquisition costs for selpercatinib and relevant comparators

Treatment	Form	Strength/unit	Pack size	Cost per pack (£)
Selpercatinib				
Selpercatinib	Capsules	80 mg	60	[redacted][a]
Selpercatinib	Capsules	40 mg	60	[redacted][a]
Pembrolizumab plus pemetrexed plus carboplatin				
Pembrolizumab	Vial	25 mg/ml	4 ml	2,630.00[b]
Pemetrexed	Powder	100 mg	1 ml	128.00[b]
Carboplatin	Vial	10 mg/ml	15 ml	6.08[c]
Pemetrexed plus platinum chemotherapy				
Pemetrexed	Powder	100 mg	1 ml	128.00[b]
Carboplatin	Vial	10 mg/ml	15 ml	6.08[c]

Based on Table 54, CS.[3]
[b]BNF 2021[50]
[c]eMIT 2021[51]
[a] Cost including PAS discount

BNF = British National Formulary 2021; eMIT = electronic market information tool 2021; PAS = Patient Access Scheme

Table 4.8: Treatment costs included in cost-effectiveness model

Treatment	Cycle length		Period 1 cost (£)	Period 2 cost (£)	Period 3 cost (£)	Period 4 cost (£)
Selpercatinib		**Week**	**0-3**	**4+**	**-**	**-**
Selpercatinib	4 weeks		[redacted][a]	[redacted][a]	-	-
Pembrolizumab plus pemetrexed plus carboplatin		**Week**	**0-2**	**3-11**	**12-103**	**104+**
Pembrolizumab	3 weeks		5,260.00	4,497.30	4,497.30	0.00
Pemetrexed	3 weeks		1,172.27	994.68	994.68	994.68
Carboplatin	3 weeks		17.49	15.46	0.00	0.00
Total			6,449.76	5,507.45	5,491.98	994.68
Pemetrexed plus platinum chemotherapy		**Week**	**0-2**	**3-17**	**18+**	**-**
Pemetrexed	3 weeks		1,172.27	994.68	994.68	-
Carboplatin	3 weeks		17.49	15.46	0.00	-
Total			1,189.76	1,010.15	994.68	-

Based on NICE TA584;[71] Planchard et al 2018;[102] Langer et al 2016;[104] Doebele et al 2015. Based on CS model, costs tab.

[a] Cost including PAS discount

CS = company submission; NICE = National Institute for Health and Care Excellence; PAS = Patient Access Scheme; TA = Technology Appraisal

4.2.9.3 Administration costs

Treatment administration and monitoring costs were based on NHS reference costs 2019/2020[52], PSSRU 2021[53], TA520[49] and TA557[54] and included 12 minutes of pharmacy time for selpercatinib, as summarized in Table 59 in the CS. During treatment with any of the three interventions, patients were assumed to have one oncologist visit every 3 weeks (consistent with TA520[49]). In addition, in alignment with the summary of product characteristics (SmPC), patients treated with selpercatinib received seven ECGs.

4.2.9.4 Subsequent treatments

The subsequent treatment distributions in the company's base-case were informed by previous NICE TAs[5,6,55] and their costs were applied at the time of disease progression as one-off cost as summarised in Table 4.9. Subsequent treatment distributions provided by the expert oncologist were used in a scenario analysis to explore their impact on the cost-effectiveness estimates.

Subsequent treatment costs included the time on treatment, associated administration costs, and the fraction of patients receiving each post-progression therapy.

Table 4.9: Subsequent treatment distributions and costs applied in the base-case analysis

Treatment	Mean cost (£)	Selpercatinib (%)	Pembrolizumab plus pemetrexed plus carboplatin/cisplatin (%)	Pemetrexed plus carboplatin/cisplatin (%)
Docetaxel	1,419	55%	100%	15%
Nivolumab	13,536	0%	0%	34%
Pembrolizumab	30,984	0%	0%	34%
Atezolizumab	16,351	0%	0%	17%
Carboplatin	1,437	0%	0%	0%
Docetaxel plus nintedanib	9,998	0%	0%	0%
Pemetrexed plus carboplatin	8,110	45%	0%	0%
BSC	9,894	0%	0%	0%
Total (one-off) costs		4,430.00	1,419.00	18,130.00

Based on CS model, costs tab and CS Table 60.[3]
BSC = best supportive care; CS = company submission

4.2.9.5 Health state costs

Health state resource use estimates were based on TA654[47] for osimertinib (CS, Table 62), which the company considered a reasonable proxy. The mean (weekly) cycle costs per for progression-free state was £74.79, whilst the per cycle costs for progressed disease was £118,10. A scenario analysis was performed in which resource use estimates were based on an expert oncologist (CS, Table 63).

4.2.9.6 Adverse event costs

Adverse event costs were calculated based on the incidence rates presented in Table 51 in the CS and applied as a one-off cost in the first model cycle. All AEs were assumed to last for a single cycle in line with previous cost-effectiveness analyses in NSCLC.

4.2.9.7 End-of-life costs

A one-off end of life cost of £4,189.76, which included hospital admission and excess bed days, Macmillan nurse home visits and hospice care stays, was included in the second line setting based on costs reported in NICE TA654.[47]

4.2.9.8 Miscellaneous unit costs

Despite the company's belief that no costs for genetic testing should be included in the analysis, a cost of £34 per tested patient was included in the company's base case as reported in NICE TA760.[42]

EAG comment:

- The main concerns of the EAG relate to a) the company's choices for the modelling of subsequent treatments, and b) errors in the economic model related to subsequent treatments.

  a) The EAG questions the company's base-case subsequent treatment distribution. The distribution of subsequent treatments in the company's base-case was informed by prior NICE TAs in NSCLC, and a scenario analysis was conducted in which subsequent treatments were informed by an expert oncologist. In response to the clarification letter, the company explained

that the subsequent treatment distribution based on previous immunotherapy appraisals was deemed more appropriate given immunotherapy (pembrolizumab combination therapy) was a main comparator for this appraisal. The EAG, however, questions the plausibility of the company's base-case approach, as it does not align with the care pathway for RET fusion-positive advanced NSCLC in NG122. According to NG122, after first line pembrolizumab combination therapy patients (regardless of their PD-L1 status) should be treated with either docetaxel as a monotherapy or in combination with nintendanib, or selpercatinib. After first line pemetrexed plus platinum chemotherapy, the NG122 recommends pembrolizumab, atezolizumab, nivolumab, docetaxel plus nintendanib and selpercatinib as subsequent treatment option. In contrast, in the company's base-case 100% of patients in the pembrolizumab combination therapy arm are assumed to receive subsequent docetaxel monotherapy and docetaxel and nintendanib combination therapy was not part of the subsequent treatment distribution for patients after pemetrexed plus platinum chemotherapy. Although selpercatinib would also be a subsequent treatment option according to NG122, the EAG agrees that second line selpercatinib should be excluded as it is currently in the CDF, as pointed out by the company in response to clarification question B21c. For the subsequent treatment distribution post selpercatinib, the company stated that estimates were based on subsequent treatments applied to other targeted treatments in non-squamous NSCLC. Considering the targeted treatments in NG122, it is unclear to the EAG how the company in the end modelled patients to receive docetaxel monotherapy and pemetrexed plus platinum chemotherapy post selpercatinib and further justification for this is necessary. In addition, although the expert oncologist expected a substantial proportion of patients to receive BSC as a subsequent treatment, it was not considered as an option in the company's base-case and the company acknowledged this to be a potential limitation in response to clarification question B21b.

In the EAG base-case, subsequent therapies after pembrolizumab combination therapy were modelled in line with NG122 and the footnote below CS, Table 61, i.e., 15% docetaxel, 50% docetaxel plus nintendanib and 35% BSC. After pemetrexed plus platinum chemotherapy, patients in the EAG base-case were modelled in line with NG122 and the values of the expert oncologist as reported in CS, Table 61. As the EAG considered the company's justification for the modelling of subsequent treatments after selpercatinib to be insufficient and it is currently unclear which subsequent treatment options would be appropriate after first line selpercatinib (given that it is currently not part of the clinical care pathway as a first-line option), the EAG would ideally inform subsequent treatments post selpercatinib based on data from the LIBRETTO-001 trial. Although the company provided these data in Table 32 of the clarification response, it was not possible for the EAG to implement these into the economic model and this analysis should therefore be explored by the company in a scenario analysis. As an alternative, the EAG, in its base-case, modelled subsequent treatments post selpercatinib in line with the expert oncologist values as reported in CS, Table 61. Given that the company did not include pembrolizumab combination therapy as a subsequent treatment option after selpercatinib in its economic model, the EAG slightly amended the expert oncologist values and modelled 5% of patients to receive subsequent atezolizumab/pembrolizumab, 75% pemetrexed plus platinum chemotherapy and 20% BSC.

b) The EAG identified two errors in the economic model related to the modelling of subsequent treatments. First, CS, Table 60 and the clinical validation meeting minutes report that in the company's base-case patients after selpercatinib are assumed to receive docetaxel or pemetrexed plus platinum chemotherapy. However, in the economic model patients received carboplatin monotherapy rather than pemetrexed plus platinum chemotherapy, which favoured the selpercatinib arm. The EAG corrected this error and modelled subsequent treatments after

selpercatinib in line with CS, Table 60 and the clinical validation minutes. Second, the EAG identified an error in the calculation of total subsequent treatment costs in all arms: the subsequent treatment costs of docetaxel plus nintendanib, pemetrexed plus platinum chemotherapy, and BSC were not included in the total subsequent treatment costs calculation. The EAG corrected this error to make sure all subsequent treatment options in the model were part of the total subsequent treatment costs calculation. The company's deterministic base-case after correcting for the two errors resulted in an incremental cost-effectiveness ratio (ICER) of £36,909 per quality adjusted life year (QALY) gained (NMB -£2,380) versus pemetrexed plus platinum chemotherapy and £6,551 per QALY gained (NMB £61,500) versus pembrolizumab combination therapy.

4.2.10 Severity

The company used the severity modifier tool developed by ScHARR and Lumanity to calculate the absolute and proportional severity modifiers (CS, Table 66). The company stated that, in line with the NICE reference case, the Hernandez-Alava 2017 study was used to inform the base-case analysis and a number of other sources were explored in scenarios (CS, Table 67). All analyses resulted in a QALY modifier of 1.2, which the company applied to the willingness-to-pay (WTP) threshold (£36,000 per QALY) in its base-case.

EAG comment: The EAG reproduced the shortfall analysis reported in CS Section B.3.5. The reported absolute and proportional QALY shortfall (CS, Table 67) and the 1.2 x QALY weight were successfully reproduced.

5. COST-EFFECTIVENESS RESULTS

5.1 Company's cost-effectiveness results

The CS base-case cost-effectiveness results (probabilistic) indicated that selpercatinib is both more effective (incremental QALYs of [redacted]) and more costly (additional costs of [redacted]) than pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively amounting to ICERs of £36,025 and £5,209 per QALY gained (CS, Table 71 and Table 5.1 below). The NHB for the probabilistic analyses was not reported in the CS, thus these were calculated by the EAG to be [redacted] and [redacted] for selpercatinib versus pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively (with a severity modifier of 1.2 on the QALY, i.e., a WTP threshold of £36,000 per QALY). Consequently, pemetrexed plus platinum chemotherapy with pembrolizumab was extendedly dominated. The probability of selpercatinib being cost-effective, at threshold values of £30,000 and £40,000 per QALY gained were estimated to be [redacted] (CS, Figure 31).

Table 5.1: Probabilistic CS base-case results

Intervention	QALYs	Costs (£)	Incremental QALYs	Incremental Costs	Incremental ICER (£/QALY)
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	
Pembrolizumab plus pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
Selpercatinib	[redacted]	[redacted]			36,025

Source: Table 71, CS.[3]
CS = company submission; ICERs = incremental cost-effectiveness ratios; QALYs = quality-adjusted life years

Overall, the technology is modelled to affect QALYs by:

- Increased PFS for selpercatinib (QALYs in the progression-free (PF) health state increased by [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively) and increased OS for selpercatinib (survival (undiscounted) increased by 4.110 and 3.361 years compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively). This resulted in post-progression benefits of [redacted] and [redacted] QALYs compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively (estimates retrieved from CS, Appendix J).
- Treatment benefit (in terms of OS and PFS) are maintained for the whole duration of the time horizon i.e., no waning of these treatment benefits.

Overall, the technology is modelled to affect costs by:

- The higher treatment costs (additional costs of [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively) and higher disease management costs (additional costs of [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively). These costs are partly offset by lower subsequent treatment costs (cost

savings of [redacted] and [redacted]compared with pemetrexed + platinum chemotherapy and pembrolizumab combination therapy respectively; estimates retrieved from CS, Appendix J).

EAG comment:

- The main concerns of the EAG relate to the extent and plausibility of the observed gains accumulated beyond the observed data period. In clarification question B23, the EAG requested the company to provide a comparison of the observed (progression-free) survival for instance using restricted mean survival time (RMST) and the undiscounted life years (LYs) as well as undiscounted progression-free LY (PFLY) estimated based on the economic model and elaborate on the plausibility of the differences. Unfortunately, the company did not provide the estimated proportion of gains accumulated beyond the observed data period for the increment. Therefore, the EAG calculated these proportions of gains accumulated beyond the observed data period (note that numbers might be subject to rounding errors). Based on clarification response Table 31 the following statements can be made:
    - The proportion of (PF)LY accumulated beyond the observed data is [redacted] for selpercatinib than for pemetrexed plus platinum chemotherapy.
    - The observed PFS for pemetrexed plus platinum chemotherapy (based on a 1.0 year or 1.5-year time horizon) is larger than the modelled PFS based on a lifetime time horizon.
    - Considering the increments, approximately [redacted] (or more depending on the truncation point) of the LYs are gained beyond the observed data period for selpercatinib compared with pemetrexed plus platinum chemotherapy while this is approximately [redacted] (or more depending on the truncation point) for PFLY.
- These findings indicate that the large majority of (PF)LY gains are accumulated beyond the observed data period and hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted (as requested but not provided in the company's response to clarification question B23). This includes verifying the plausibility of the partitioned survival model extrapolations (see Section 4.2.2).
- In addition to the above, it is noticeable that the observed PFS for pemetrexed plus platinum chemotherapy (based on a 1.0 year or 1.5-year time horizon) is larger than the modelled PFS based on a lifetime time horizon. This might suggest that PFS for pemetrexed plus platinum chemotherapy is underestimated and hence the increments versus selpercatinib potentially overestimated (see Section 4.2.6).

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses.

The parameters that have the greatest effect on the ICER (based on the company's DSAs) were:

- Discount rate for costs
- Discount rate for outcomes
- Drug administration costs
- Subsequent active systemic anticancer therapy costs
- Drug related monitoring costs
- AE costs

Based on the company's scenario analyses, modelling assumptions that have the greatest effect on the ICER were related to:

- Estimation of TTD
- Estimation of PFS
- Estimation of OS
- Subsequent therapy distribution
- Assuming alternative utility values (from TA654)

EAG comment:

- The main concerns of the EAG relate to a) the runtime of the probabilistic analyses and b) counterintuitive deterministic sensitivity analyses results (CS, Figures 32 and 33).

  a) The PSA requires a relatively long run time (as also mentioned in CS, Section B.3.10.3) which hampers the EAG to perform analyses. Unfortunately, according to the company, there are no straightforward adjustments that were found to speed up the run time of the probabilistic analyses (response to clarification question B28).
  b) The CS, Figures 32 and 33 (tornado diagram) included counterintuitive results (which was due to an error as indicated in response to clarification question B27). The company provided corrected tornado diagrams, see clarification response B27 (Figure 20 and Figure 21).

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The model structure, source data and statistical analysis design were reviewed by external experts, including a health economist and UK clinical experts in NSCLC. The company noted that considering the currently immature OS data available from the LIBRETTO-001 trial, a thorough clinical validation process was conducted in order to inform survival analysis for the OS extrapolations selected for the base case analysis. Moreover, the company stated that clinical feedback was also used to validate the resource use inputs utilised in the model, including subsequent treatment choices and monitoring frequencies.

5.3.2 Technical verification

According to the CS, quality-control procedures for verification of input data and coding were performed by health economists not involved in the model development and in accordance with a pre-specified test plan. These procedures included verification of all input data with original sources and programming validation. Verification of all input data was documented (with the initials of the health economist performing the quality-control procedure and the date the quality-control procedure was performed) in the relevant worksheets of the model. Any discrepancies were discussed, and the model input data was updated where required. Programming validation included checks of the model results, calculations, data references, model interface, and Visual Basic for Applications code.

5.3.3 Comparisons with other technology appraisals

No comparisons with other TAs were reported in CS, Section B.3.13 (reporting on validation). However, the company stated that where possible, UK sources were used for model inputs and similar inputs and approaches to those used in prior appraisal were adopted. This includes the adoption of the cohort-based partitioned survival model approach, in line with a number of prior NICE appraisals in

NSCLC, including TA683[21], TA705[7] and TA760[42]. Moreover, CS, Table 36 provides and overview of features of the economic analysis compared with TA654[47], TA683[21], TA760[42] and TA812.[56]

5.3.4 Comparison with external data used to develop the economic model

According to the company, it was not possible to conduct external validation of model outcomes for selpercatinib against trial data as the median PFS and OS were not yet reached in the LIBRETTO-001 trial for the SAS1 population.

5.3.5 Comparison with external data not used to develop the economic model

Clinical feedback was used to validate the curve choices to extrapolate the trial data over the lifetime time horizon of the model. In addition, model estimates for median PFS and OS for selpercatinib were consistent with real-world data obtained in RET fusion-positive NSCLC patients receiving selective tyrosine kinase inhibitor (TKI) in clinical practice (CS, Table 73). Model estimates for median PFS and OS for both pembrolizumab combination therapy and pemetrexed plus platinum-based chemotherapy were also found to be consistent with estimates obtained during the phase III KEYNOTE trial in untreated, metastatic non-squamous NSCLC patients (CS, Table 73).

EAG comment: The main concerns of the EAG relate to the technical verification provided by the company. The EAG asked to company to complete the TECH-VER checklist to support the technical verification of the economic model (clarification question B27). This was not provided by the company. According to the company the checklist used by the company was derived based on the TECH-VER checklist and thus provided the same verification of validity as the TECH-VER checklist. This seems reasonable to the EAG (though the EAG is unable to verify this as the company's checklist was not provided in response to clarification question B27).

6. EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost-effectiveness categorised according to the sources of uncertainty as defined by Grimm et al 2020[57]:

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost-effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler et al 2016[58]:

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong).
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to).
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

1. Subsequent treatment costs of docetaxel plus nintendanib, pemetrexed plus platinum chemotherapy, and BSC were not included in the total subsequent treatment costs calculation (Section 4.2.9).
   The error was corrected by including all subsequent treatment options in the model to the total subsequent treatment costs calculation.
2. Inconsistency in subsequent treatment distribution after selpercatinib between the CS/clinical validation minutes (docetaxel or pemetrexed plus platinum chemotherapy) and the economic model (docetaxel or carboplatin monotherapy) (Section 4.2.9).

The error was corrected by modelling subsequent treatments after selpercatinib in line with the CS and the clinical validation minutes.

6.1.1.2 Fixing violations

No FVs were identified by the EAG.

6.1.1.3 Matters of judgement

3. Progressed disease utility based on TA654 (Section 4.2.8).
   The progressed disease utility from TA654 was used instead of the progressed disease utility informed by the LIBRETTO-001 trial.
4. Subsequent treatment distribution and values based on NG122 and expert oncologist inputs (Section 4.2.9).
   Subsequent treatment distribution and values for all arms were based on NG122 and expert oncologist inputs instead of based on previous immunotherapy appraisals.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Scenario analyses – impact of data immaturity and lack of transparency

To reflect the uncertainty due to data immaturity, and resulting ambiguity in choice of survival curves, the EAG conducted scenario analyses to find the range of results given plausible parametric survival curves. To do so, a set of plausible scenarios was defined and results of the most and least beneficial plausible survival curves for OS and PFS for each comparator individually were reported.

Plausibility was defined by:

a) Being closer to an expert estimate or external source than the curve chosen by the company.
b) The curve having a plausible shape.

For both comparators, the lognormal curves were excluded as they produced clinically implausible tails with almost 8% and 2% patients surviving at 10 and 20 years. Further, in the pemetrexed plus platinum chemotherapy comparison, the spline knot 3 curve was excluded for PFS, as the curve had an implausible shape (PFS increasing).

Based on this, for the comparison with pembrolizumab combination therapy, the exponential, and Gompertz curves were considered for PFS and the exponential, spline knot 2 and stratified Gompertz curves were considered for OS. For the comparison with pemetrexed plus platinum chemotherapy, the exponential, and Gompertz curves were considered for PFS and the stratified lognormal, lognormal, exponential, loglogistic, spline knot 2 and stratified Gompertz curves were considered for OS.

Please note that there was a mismatch between the modelled PFS, and OS values as reported in the CS and the actual values used in the economic model (see Section 4.2.6. critique b) d.). The EAG scenario analyses to explore the impact of data immaturity and lack of transparency were conducted based on the values reported in the CS. The following are the exploratory scenario analyses:

5. Survival curves with highest NMB (Section 4.2.6).
   The EAG selected the exponential curve for PFS and OS in both arms.
6. Survival curves with lowest NMB (Section 4.2.6).
   The EAG selected the Gompertz curve for PFS in both arms and the stratified Gompertz curve for OS in both arms.

7. Progression-free and progressed disease utility based on TA654 (Section 4.2.8).
   The EAG selected the progression-free and progressed disease utilities from TA654 instead of the progression-free and progressed disease utilities informed by the LIBRETTO-001 trial.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost-effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties in the extrapolation period	4.2.2	Methods	Compare results of PSM to the outcomes of a STM	+/-	No	Use of STM to assist in verifying the plausibility of PSM extrapolations
The data obtained from the LIBRETTO-001 trial for OS and PFS is immature, adding substantial uncertainty to the extrapolated survival data in the economic model	4.2.6	Imprecision	Scenario analyses to find range of results given plausible parametric survival curves	+/-	No	Long-term PFS and OS data to reduce the uncertainty around the cost-effectiveness results
The company's choice of survival curves for the modelling of treatment effectiveness was not transparent	4.2.6	Transparency	More details concerning the choice of parametric survival curves	+/-	No	More information about a) the choice of considering complex survival curves, b) plots not provided in the clarification response c) the choice between survival curves in detail and d) the mismatch between reported PFS and OS values in the CS and the economic model
No treatment waning was explored	4.2.6	Bias and indirectness	Hazard ratio plots for PFS and OS versus time	+/-	No	Hazard ratio plots for PFS and OS versus time. Scenario analyses to explore the impact of

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
			Scenario analyses to explore the impact of treatment waning into the model			treatment waning into the model
The observed PFS for pemetrexed plus platinum chemotherapy is larger than the modelled PFS. This might suggest that PFS for pemetrexed plus platinum chemotherapy is underestimated and hence the increments versus selpercatinib potentially overestimated	4.2.6 and 5.1	Bias and indirectness	Alternative approaches to estimate PFS for pemetrexed + platinum chemotherapy where the modelled PFS > observed PFS for pemetrexed + platinum chemotherapy	+	No	Long-term PFS data.
Utility values in the company's base-case were higher than the ones used in other TAs, only slightly lower than the UK general population, and had a relatively small decrement between PF and PD states	4.2.8	Bias and indirectness	Scenario analyses exploring utility values from other relevant TAs. PD utility from TA654	+	Yes	N/A

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
The plausibility of the company's choices for the modelling of subsequent treatments	4.2.9	Methods	Informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial. Informing subsequent treatments for the comparators based on NG122 and expert oncologist input	+/-	Partly	A scenario analysis informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator

[b] Explored

CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; OS = overall survival; PD = progressive disease; PF = progression-free; PFS = progression-free survival; PSM = partitioned survival model; STM = state transition model; TAs = Technology Appraisals; UK = United Kingdom

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

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the EAG base-case. The submitted model file contains technical details on the analyses performed by the EAG (e.g., the "EAG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic/probabilistic EAG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
CS base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,883	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,264	[redacted]	[redacted]
Fixing error (1-Error in calculation of total subsequent treatment costs)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,883	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,264	[redacted]	[redacted]
Fixing error (2-Inconsistency subsequent treatment after selpercatinib)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,662	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£4,987	[redacted]	[redacted]
Matter of judgement (3-PD utility based on TA654)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£38,478	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£6,859	[redacted]	[redacted]
Matter of judgement (4-Subsequent treatments based on NG122 and expert oncologist)							
Selpercatinib	[redacted]	[redacted]					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£40,467	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,347	[redacted]	[redacted]
Deterministic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,187	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,599	[redacted]	[redacted]
Probabilistic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,230	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,535	[redacted]	[redacted]

[1] ICER versus selpercatinib; [2] iNMB and iNHB for WTP of £36,000 per QALY

CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; iNMB = increment net monetary benefit; NG122 = NICE guideline 122; PD = progressed disease; QALY = quality adjusted life year; TA = Technology Appraisal; WTP = willingness-to-pay

Table 6.3: Deterministic scenario analyses (conditional on EAG base-case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Deterministic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,187	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,599	[redacted]	[redacted]
Scenario analysis (5-Survival curves with highest NMB)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£38,970	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£4,442	[redacted]	[redacted]
Scenario analysis (6-Survival curves with lowest NMB)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£60,969	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	-£6,963	[redacted]	[redacted]
Scenario analysis (7-PF and PD utility based on TA654)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed plus platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,407	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,626	[redacted]	[redacted]

[1] ICER versus selpercatinib; [2] iNMB and iNHB for WTP of £36,000 per QALY

EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; iNMB = increment net monetary benefit; NMB = net monetary benefit; PF = progression-free; PD = progressed disease; QALY = quality adjusted life year; TA = technology appraisal; WTP = willingness-to-pay

6.3 EAG's preferred assumptions

The estimated EAG base-case ICERs (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, were £42,230 and £5,535 per QALY gained for selpercatinib versus pemetrexed plus platinum chemotherapy and the pembrolizumab combination therapy respectively. The probabilistic EAG base-case analyses indicated cost-effectiveness probabilities of 0.0% and 1.5% at WTP thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustments were using the PD utility from TA654 and informing subsequent treatments based on NG122 and expert oncologist inputs. The ICER increased most in the scenario analyses with alternative assumptions regarding the modelling of PFS and OS.

6.4 Conclusions of the cost-effectiveness section

The company's cost-effectiveness model partly complied with the NICE reference case. Deviations from the NICE reference case related to the lack of systematic reviews to identify HRQoL and resource use and costs studies, and it was unclear to the EAG whether the UK tariff was used to value HRQoL. The most prominent issues highlighted by the EAG were: 1) the lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties in the extrapolation period, 2) immaturity of PFS and OS data from the LIBRETTO-001 trial, adding substantial uncertainty to the extrapolated survival data in the economic model, 3) the lack of transparency in the company's choice of survival curves, 4) the lack of exploring potential waning of the selpercatinib treatment effect, 5) the use of relatively high utility values with a small progressed disease decrement, 6) the plausibility of the

modelled subsequent treatments in the company's base-case, and 7) potential underestimation of the modelled PFS in the pemetrexed plus platinum chemotherapy arm.

First, the EAG was concerned about the lack of a STM to verify the plausibility of the company's PSM extrapolations and to explore key clinical uncertainties in the extrapolation period as recommended by NICE DSU TSD19. The PFS and OS data for selpercatinib from LIBRETTO-001 were relatively immature, and the large majority of modelled (PF)LY gains were accumulated beyond the observed data period. Hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted. To assist in verifying the plausibility of the partitioned survival model extrapolations, the EAG would like to see the outcomes of a state transition model.

Second, the relatively immature data from the LIBRETTO-001 trial informing the PFS and OS of selpercatinib added substantial uncertainty to the extrapolated survival data in the economic model. In addition to the company's scenario analyses in the CS, the EAG conducted scenario analyses to explore a range of plausible PFS and OS curves. These scenario analyses resulted in a wide range of NMBs, confirming the substantial uncertainty surrounding the extrapolated survival data.

Third, the EAG considered the company's choice of survival curves for the modelling of treatment effectiveness in the health economic model not transparent. It was unclear to the EAG why the company selected a spline model for the modelling of OS rather than a standard parametric model, and the company did not provide plots of the standard normal quartiles versus log time and log survival odds versus log time to examine the diagnostics of the parametric survival models based on the observed data. In addition, although the company preferred expert inputs over statistical and visual fit of the parametric survival curves to the KM data to inform the choice of survival curve, it was unclear to the EAG why the company did not always select the curve closest to the expert inputs. Next to that, the modelled PFS and OS values as reported in the CS did not match with the values informing PFS and OS in the economic model for several survival curves, including the company's base-case. These transparency issues, in addition to the immaturity of the LIBRETTO-001 trial data, add substantial uncertainty to the extrapolated PFS, OS, and TTD.

Fourth, the company assumed that there was no waning of the selpercatinib treatment effect in its base-case. The company stated that there was no evidence of relative treatment waning in the single-arm LIBRETTO-001 trial for selpercatinib. The EAG requested further justification as to why no treatment waning was considered and requested hazard ratio plots for PFS and OS versus time for both comparisons (not provided), as well as an updated economic model and scenario analyses exploring treatment waning kicking in at different time points (not provided). The EAG would like to stress that these analyses are important for the assessment of the potential impact of treatment waning on the cost-effectiveness results, especially given that the current PFS and OS data are immature.

Fifth, utility values to inform the company's base-case (PF = [redacted], PD = [redacted]) were higher than the ones used in other relevant TAs, and only slightly lower than the age and gender matched UK general population norm (0.819). Moreover, the decrement for disease progression ([redacted]) seems relatively small. The company justified the high utility values and small progressed disease utility decrement with the fact that patients in the SAS1 population of the LIBRETTO-001 were younger than patients in other NSCLC TAs and were mainly non-smokers. The number of completed post-progression HRQoL questionnaires to inform PD utility was limited ([redacted] observations) and data were collected early after patients progressed, which may have led to an overestimation of the PD utility. Therefore, the EAG preferred to inform their base-case using the PD utility (0.678) from TA654. Additionally, the EAG explored a scenario analysis with both PF (0.794) and PD utility values from TA654.

Sixth, the distribution of subsequent treatments in the company's base-case was informed by prior NICE TAs in NSCLC. The EAG, however, questions the plausibility of the company's base-case approach, as it does not align with the care pathway for RET fusion-positive advanced NSCLC in NG122. Several second-line subsequent treatment options in NG122 for patients in the comparator arms were not modelled in the company's base-case. Subsequent treatments post selpercatinib were based on subsequent treatments applied to other targeted treatments in non-squamous NSCLC. Considering the targeted treatments in NG122, it was unclear to the EAG why the company in the end modelled patients to receive docetaxel monotherapy and pemetrexed plus platinum chemotherapy post selpercatinib and further justification for this is necessary. In addition, although the expert oncologist expected a substantial proportion of patients to receive BSC as a subsequent treatment, it was not considered as an option in the company's base-case. Therefore, the EAG in its base-case modelled subsequent treatments for the comparators in line with NG122 and expert oncologist inputs (CS, Table 61). The EAG would ideally inform subsequent treatments post selpercatinib based on data from the LIBRETTO-001 trial, and although the company provided these data, it was not possible for the EAG to implement these into the economic model. As an alternative, the EAG modelled subsequent treatments post selpercatinib in line with the expert oncologist values.

Finally, the EAG was concerned that the modelled PFS in the pemetrexed plus platinum chemotherapy arm is potentially underestimated. Clarification response Table 31 showed that the observed PFS for pemetrexed plus platinum chemotherapy was larger than the modelled PFS based on a lifetime time horizon. This might suggest that PFS for pemetrexed plus platinum chemotherapy was underestimated and hence the increments versus selpercatinib potentially overestimated.

The CS base-case probabilistic ICERs versus pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy were £5,209 and £36,025 per QALY gained, respectively. The estimated EAG base-case ICERs (probabilistic) versus pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy, based on the EAG preferred assumptions highlighted in Section 6.1, were £5,535 and £42,230 per QALY gained, respectively. The most influential adjustments were using the PD utility from TA654 and informing subsequent treatments based on NG122 and expert oncologist inputs. The ICER increased most in the scenario analyses with alternative assumptions regarding the modelling of PFS and OS.

In conclusion, there is large remaining uncertainty about the effectiveness and cost-effectiveness of selpercatinib, which can be partly resolved by the company by conducting further analyses. This includes providing outcomes of a STM to assist in verifying the plausibility of the PSM extrapolations, more transparency/details concerning the choice of parametric survival curves, scenario analyses exploring potential waning of the selpercatinib treatment effect, and a scenario analysis informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial. Mature long-term selpercatinib PFS and OS data would help to reduce the uncertainty surrounding the extrapolated survival data. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of selpercatinib compared with relevant comparators.

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Single Technology Appraisal

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]

EAG report – factual accuracy check and confidential information check

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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 Wednesday 30 November 2023** 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.

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Section 1: Corrections and clarifications

Issue 1 Availability of data on the UK target population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 1.1 on Page 14 states: "Applicability: there is no information on the characteristics of the UK target population, meaning that comparability between trial and target population cannot be assumed." Table 1.6 on Page 18 states: "There is no information on the characteristics of the UK target population, meaning that comparability between trial and target population cannot be assessed" And "Provide characteristics of the UK target population." Page 87 states: "The EAG does not think that the international data provided by the	Please amend as follows: On Page 14: "Applicability: there is **limited** information on the characteristics of the UK target population, meaning that comparability between trial and target population cannot be assumed" On Page 18 "There is **limited** information on the characteristics of the UK target population, meaning that comparability between trial and target population **is difficult** to assess" And "Provide **more** characteristics of the UK target population" On Page 87 "The EAG does not think that the **UK** data provided by the company is at all helpful in illustrating the	For amendments on Page 14 and 18: The Company provided some characteristics on the UK target population obtained from a real-world survey in response to Clarification Question A.18. These characteristics were found to be broadly in alignment with the baseline characteristics of patients in the SAS1 population of the LIBRETTO-001 trial.. For amendments on Page 87: In response to Clarification Question A.18 the Company provided data on 74 patients with treatment-naïve RET fusion positive advanced NSCLC in the UK. Therefore, stating the data provided were international is factually inaccurate. For amendments on Page 124: As noted above, baseline characteristics data for 74 patients in	This has been amended – we have re-written the relevant sections.

company is at all helpful in illustrating the characteristics of the UK target population." Page 124 states: "The lack of data on the characteristics of the UK target population means that it cannot be assumed that the trial participants were comparable to the target population."	characteristics of the UK target population because…." On Page 12: "The limited data on the characteristics of the UK target population mean that it cannot be assumed that the trial participants were comparable to the target population. However, the limited data available was found to be broadly generalisable to the SAS1 population of LIBRETTO-001."	the UK target population were provided in response to Clarification Question A.18. As such, this wording that there are no available data on the UK target population is factually inaccurate. In addition, it should be noted that baseline characteristics of the SAS1 population were broadly generalisable to the UK target population, based on these available data.	

Issue 2 Costs associated with selpercatinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15 states: "The higher drug costs (additional costs of ******* and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively)…"	Please amend as follows: "The higher ~~drug~~ **treatment** costs (additional costs of [redacted] and [redacted] compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively)…."	The costs quoted here relate to the total cost of treatment and therefore incorporate drug administration, adverse event and monitoring costs as well as drug acquisition costs.	Amended

Issue 3 Effect of subsequent treatment distributions on the ICER

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 1.4 on Page 17 states: "ICER probably underestimated either due to bias in effectiveness of cost."	Please amend as follows: "ICER **may be** underestimated **or overestimated** due to bias in **either** effectiveness **or** cost."	Changing the distribution of subsequent therapies could impact the ICER in either direction. Indeed, the results of the EAG scenario analysis exploring this resulted in a reduction in the ICER for selpercatinib versus both relevant comparators (see Table 6.2 of the EAG report). The current phrasing in the EAG report is therefore misleading and should be amended in line with the proposed suggestion.	Not a factual inaccuracy

Issue 4 Number of patients receiving subsequent treatments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 1.4 on Page 17 states: "pembrolizumab plus pemetrexed and platinum chemotherapy: 10 to 15% might have received pembrolizumab in some combination versus. 5%."	Please amend as follows: "pembrolizumab plus pemetrexed and platinum chemotherapy: around [redacted] might have received pembrolizumab in some combination with chemotherapy versus. 5%." Or "pembrolizumab plus pemetrexed and platinum chemotherapy: **the proportion of patients who received pembrolizumab combination therapy in the LIBRETTO-001 trial was**	The values given in the EAG report are produced by summing all treatments involving pembrolizumab post LIBRETTO-001 trial, rather than specifically pembrolizumab in combined chemotherapy as estimated by experts. As such, these numbers should be replaced by data provided in response to Clarification Question A.20, which represent the proportion of patients	The EAG cannot work out how the [redacted] has been calculated. Indeed, the EAG reproduced Table 32 from the clarification letter response to attempt to calculate the percentages in LIBRETTO-001, which is very difficult given that the categories in the left-hand column of that table are not mutually exclusive and do not clearly

	broadly aligned with the subsequent therapy distributions suggested by clinical experts ([redacted]versus 5%, respectively)"	who subsequently received pembrolizumab in combination with chemotherapy after LIBRETTO-001. All percentages for subsequent therapies from the LIBRETTO-trial are academic in confidence and thus should be highlighted accordingly.	distinguish mono- from combination therapies. Therefore, given the continued lack of clarity, no change has been made to the EAG report.

Issue 5 Impact of the progression-free life years associated with pemetrexed plus platinum chemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 1.16 on Page 23 states: "Based on the Company Submission scenario analyses (as summarised in Section 5.2 of this report), PFS was amongst the modelling assumptions that have the greatest effect on the ICER."	Please amend as follows: "Based on the Company Submission scenario analyses (as summarised in Section 5.2 of this report), PFS was amongst the modelling assumptions that have the greatest effect on the ICER **for selpercatinib versus pembrolizumab combination therapy.**"	The results of the scenario analyses presented in the Company submission found PFS was amongst the modelling assumptions that had the greatest effect on the ICER for comparisons versus pembrolizumab combination therapy. However, this was not the case for pemetrexed plus platinum chemotherapy: the scenario analyses exploring the curve choice for PFS for comparisons versus pemetrexed plus platinum chemotherapy resulted in a maximum change to the ICER of +/- 1.3%. As such, this statement should be amended as suggested for accuracy and clarity.	Not a factual inaccuracy

Issue 6 Population addressed in the Company Submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 2.1 in Section 2, Page 27 describes the relevant population for this appraisal as: "treatment-naïve patients with advanced non-squamous *RET* fusion-positive NSCLC who require systemic therapy". AND Page 129 states: "The population considered in the Company Submission was treatment-naïve patients with advanced non-squamous *RET* fusion-positive NSCLC who require systemic therapy."	Please amend as follows: Page 27: **"Advanced *RET* fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor."** Page 129: "The population considered in the Company Submission was **advanced *RET* fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor."**	As noted in response to Clarification Question A.7, the population wording currently presented by the EAG was added to reflect the anticipated marketing authorisation for the indication under appraisal. Further to this, Lilly can now confirm that this license extension was granted by the MHRA on 26th October 2022, and that the licence for selpercatinib is "for the treatment of adults with advanced *RET* fusion-positive NSCLC not previously treated with a RET inhibitor".[1] The population wording should be updated throughout the EAG report to reflect this change.	The original decision problem described in the CS is the basis on which the company's submission was written. Therefore, changing the decision problem definition at this point (after the analyses based upon the original definition have been submitted) is not appropriate. The EAG has added a note to the first Key Issue regarding the population to highlight the discrepancy between the license extension and the scope/decision problem.

Issue 7 Comparators addressed in the company submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 2.1 on Page 27 states: "The company argue that the excluded comparators…are not used frequently enough according to clinical expert opinion. This is despite these treatments beings recommended by the NICE guideline NG122. A stronger rationale is required for a decision that could have a profound effect on clinical and cost-effectiveness."	Please amend as follows: "I**n alignment with feedback provided by UK clinical experts as part of the recent appraisal of pralsetinib in the same indication,** the company argue that the excluded comparators … are not used frequently enough according to clinical expert opinion. This is despite these treatments being recommended by the NICE guideline NG122. A stronger rationale is required for a decision that could have a profound effect on clinical and cost-effectiveness."	It should be highlighted that pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy representing the main treatments used in the target population in the UK is supported by UK clinical experts in a recent and relevant NICE appraisal.	Not a factual inaccuracy

Issue 8 The inclusion of pemetrexed plus platinum chemotherapy as a comparator

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 33 states: "Pemetrexed plus platinum chemotherapy is included as a comparator even though it was not included in the scope for non-squamous histology."	This statement should be removed	As clarified in response to Clarification Question A.9, pemetrexed with platinum chemotherapy is included in the NICE scope for patients with non-squamous histology in the list of comparators for patients with adenocarcinoma. As outlined in Section B.1.2.1 of the Company	Amended

		Submission, adenocarcinoma and large cell undifferentiated carcinoma are considered together under "non-squamous" histology.[2] As such, this statement is factually inaccurate and should be removed.	

Issue 9 Terminology used for SLR2 (additional comparators)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 36 and throughout Section 3.1.1, it is stated: "Two additional searches were conducted to incorporate new comparator interventions in June 2018 (SLR2 targeted) and August 2020 (SLR3b)."	Please amend this wording as follows in all relevant instances: "Two additional searches were conducted to incorporate new comparator interventions in June 2018 (SLR2**: additional comparators**) and August 2020 (SLR3b)."	This is how the additional SLR2 search is termed in the Company Submission and its appendices.	Amended

Issue 10 Cochrane-associated literature searches

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Row 5 of Table 3.1 on Page 36 states that host-source of the evidence-based medicine reviews was: "Not reported".	Please amend as follows: "**Cochrane Central Register of Controlled Trials (CENTRAL)"** for the central column.	CENTRAL is a valid host/source reported in the Company Submission.	While CENTRAL is the name of a database, it is not the name of the host which provides access to the database. The host could potentially be either Wiley (via the Cochrane Library) or Ovid.

Issue 11 Conference Proceedings literature search date range

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Row 12 –17 of Table 3.1 on Page 36 states the data ranges for the conference proceedings are: "Not reported".	Please amend to: "2014 –Q2 2022"	The date range for the conference proceedings searches was provided in the Company submission.	Amended

Issue 12 Inclusion/exclusion criteria of the clinical SLR updates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 41 it states: "As a further example, the dates of the four SLR updates are given, but no information is given on the nature of these updates. It is unclear if these updates were simply 're-runs' or if changes were made to the inclusion/exclusion criteria of the protocol on each update"	This statement should be removed	The eligibility criteria provided in Table 25 in Appendix D.1.2 of the Company Submission are applicable to all searches, as evidenced by the timeframe row containing dates for all searches (SLR1–SLR5). Lilly apologise if this was unclear to the EAG but request this statement be removed given this clarification.	Not a factual inaccuracy

Issue 13 Exclusion criteria of the LIBRETTO-321 trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 3.8 on Page 55, in the exclusion criteria for participants in the LIBRETTO-321 trial it states: "Concurrent use of drugs prolonging QTc, active secondary malignancy"	Please amend as follows: "Concurrent use of drugs prolonging QTc **A**ctive secondary malignancy"	Beginning a new line prior to "active secondary malignancy" and removing a comma would clarify that it is a distinct exclusion criterion to concurrent use of drugs prolonging QTc.	Amended

Issue 14 Subsequent therapy distribution in LIBRETTO-001 versus clinical expert opinion

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 66 states: "However, as the company point out, there is a large discrepancy between Table 61 and Table 3.16: Table 61 shows that clinical experts believe the following distribution (%) applies to clinical practice."	Please amend as follows: **"The Company identified similarities between the two distributions in the proportion of patients receiving docetaxel or docetaxel plus nintedanib. However, several differences between the two distributions were also identified**; Table 61 shows that clinical experts believe the following distribution (%) applies to clinical practice."	In response to Part B of Clarification Question A.20 Lilly identified both similarities and differences between the subsequent treatment distributions included in the base case analysis versus those in LIBRETTO-001. To provide a balanced account, the similarities in these data should also be commented on.	Not a factual inaccuracy

Issue 15 Subsequent therapy bias

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 66 states: "If there is a mismatch between the trial and NHS clinical practice, this could lead to two potential biases i.e., in effectiveness if a higher proportion of more effective immunotherapy combination treatments were administered in the trial, and in cost if the economic model	Please amend as follows: "If there is a mismatch between the trial and NHS clinical practice, this could lead to two potential biases i.e., in effectiveness if a **differing** proportion of more effective immunotherapy combination treatments were administered in the trial, and in cost if the economic model assumed the **differing** proportion of those treatments."	Changing the distribution of subsequent therapies utilised in the economic model has the potential to bias results either in favour of OR against selpercatinib and therefore this should be made clear in the EAG report.	Not a factual inaccuracy

assumed the lower proportion of those treatments.”			

Issue 16 Brain metastases point estimates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 86 states: “The point estimates in Figure 3.5 do not appear to support the notion that the efficacy of selpercatinib is independent of the existence of brain metastases, as a clear difference in ORR point estimates exists between the sub-groups”	Please amend as follows: “The point estimates in Figure 3.5 do not appear to support the notion that the efficacy of selpercatinib is independent of the existence of brain metastases, as a clear difference in ORR point estimates exists between the sub-groups, **although it should be noted that these results are not statistically significant**.”	For transparency and to aid interpretation of results, it should be made clear that the observed differences in points estimates are not statistically significant.	We had already acknowledged the statistical uncertainty in the subsequent sentence: “Although there is probably some uncertainty, the analysis was almost certainly underpowered to detect a significant difference in effect between the sub-groups, and so the prudent response to this would be to state that a type II error may be responsible for the ‘lack of significance’, and that a true sub-group difference may exist (even if undetected as a statistically significant effect).”

Issue 17 Potential treatment effect modifiers

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 87 states: "The EAG regards the incomplete sub-group analysis for 'race' to prohibit the assumption that race is not an outcome modifier." AND "Meanwhile, the sub-group analyses demonstrated that CNS metastases, age and ECOG may be effect modifiers, and the incomplete sub-group analysis of 'race' means that 'race' cannot be excluded as an effect modifier." Page 113 states: "Brain metastases were also associated with worse prognosis, having been identified as prognostic in the CS,[3] and having potential for treatment effect modification as revealed by subgroup analysis of LIBRETTO-001 (see Section 3.2.6)"	Please amend as follows: Page 87: "The EAG regards the incomplete sub-group analysis for 'race' to prohibit the assumption that race is not an outcome modifier. **However, the results that are available from the incomplete sub-group analysis suggest that race is not a treatment effect modifier and that results from a full subgroup analyses may not improve clarity on this matter given they would be subject to significant uncertainty owing to the low patient numbers available."** AND "Meanwhile, the sub-group analyses demonstrated that CNS metastases, age and ECOG may be effect modifiers, **although none of the results of the subgroup analyses were found to be statistically significant,** and the incomplete sub-group analysis of 'race' means that 'race' cannot be excluded as an effect modifier." Page 113: "Brain metastases were also associated with worse prognosis, having been identified as prognostic in the CS,[3] and having potential for treatment effect modification as revealed by subgroup analysis of LIBRETTO-001, **although it should be highlighted that the results of the subgroup analyses were**	For transparency and accuracy of interpretation, it should be noted that these results of the subgroup analyses were not statistically significant.	For the first point (p87) there is no factual inaccuracy. For the second point we have added the point that no statistical significance was achieved, but that statistical significance/ non-significance is not informative in an analysis that was not sufficiently powered. For the third point (p113, which is now on p114) we have made the same point as above. Note that we had also made use of qualifiers such as 'may' and 'potential' in the original text to capture the uncertainty.

	not statistically significant (see Section 3.2.6)"		

Issue 18 Safety analysis sets

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 95 states: "There are no specific adverse event data for the treatment naïve sub-set (SAS1 dataset). This is a potential problem as it is, as it is not possible to exclude a greater concentration of AEs in this sub-group than are observed overall. This has been deemed a key issue."	Please amend as follows: "**The safety data presented in the** Company Submission **are derived from two safety analysis sets. The overall safety analysis set (OSAS; N=796), included all patients, regardless of tumour type, while the NSCLC Safety Analysis Set (SAS; N=356) included all NSCLC patients. As such, these data are sourced from a much larger safety population than if the SAS1 (N=69) population alone had been analysed, thereby increasing the likelihood of rare events being captured and providing a more comprehensive overview of the selpercatinib safety profile. However,** there are no specific adverse event data for the treatment naïve sub-set (SAS1 dataset). This is a potential problem as it is, as it is not possible to exclude a greater concentration of AEs in this sub-group than are observed overall. This has been deemed a key issue.	For transparency, the strengths of the safety analysis sets utilised in the LIBRETTO-001 trial should be provided alongside the weaknesses. This amendment should be implemented throughout the EAG report.	Not a factual inaccuracy

Issue 19 Specifying mean or median age cited from the KEYNOTE-189 trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 3.35 on Page 100, the mean ages of patients in the PEM + (CARB or CIS) + PEMBRO and PEM + (CARB or CIS) arms of the KEYNOTE-189 trial are reported as 65.0 and 63.5 years, respectively.	Please amend as follows: These values should be updated to "65.0 **median**" and "63.5 **median**".	In Gandhi *et al.* (2018), these values are reported as median values, so their current reporting as means in the EAG report is factually inaccurate.	Amended

Issue 20 Absent footnote relating to data from the KEYNOTE-189 trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 3.35 on Page 100, a footnote [a] has been added to data from the PEM + (CARB or CIS) arm of the KEYNOTE-189 trial, but no footnote wording has been provided.	Please amend as follows: Wording for the footnote should be added, or footnote [a] deleted.	This wording is currently missing.	Amended

Issue 21 Generation of the pseudo control arm

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 103 states: "The EAG is concerned that the rationale for the choice of comparator is an administrative	These statements should be amended to clarify that this approach was taken as a necessity:	As stated in Section B.2.8.1 of the Company submission and in response to Clarification Question A.21, data from the pemetrexed plus platinum chemotherapy arm of	Amended as suggested for all 3 points

reason rather than one that would make the use of other comparators inappropriate or impossible." Page 112 states: "Another one of the three included trials that could have been considered for the ITC is KEYNOTE-021, which seems to have baseline characteristics that might be similar those of KEYNOTE-189 (See Section 3.3.1)." Page 123 states: "The choice of using the pemetrexed plus platinum chemotherapy data from the KEYNOTE-189 RCT as the pseudo-comparator arm seems to be arbitrary and a convincing rationale is not provided."	Page 103: "The EAG is concerned that the rationale for the choice of comparator is an administrative reason rather than one that would make the use of other comparators inappropriate ~~**or impossible**~~." Page 112: "Another one of the three included trials that could have been considered for the ITC is KEYNOTE-021, which seems to have baseline characteristics that might be similar those of KEYNOTE-189 (See Section 3.3.1), **although the necessary IPD data are not available from any of the other included studies**." Page 123: "The choice of using the pemetrexed plus platinum chemotherapy data from the KEYNOTE-189 RCT as the pseudo-comparator arm **is stated as being due to relevant IPD not being available from any other sources, which the EAG consider** to be arbitrary and **not** a convincing rationale ~~**is not provided**~~."	the KEYNOTE-189 trial was used to generate the pseudo control arm as it was the only arm out of the included studies of relevant comparators which had available IPD. As such, use of data from other comparators, including the KEYNOTE-021 trial mentioned, to generate the pseudo control arm was impossible. As such, these statements as currently presented in the EAG report are factually inaccurate and should be updated for accuracy.	

Issue 22 Technique used to adjust for confounding

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 113 states: "Such a preferable method might produce results that demonstrate less of a benefit for selpercatinib than observed in the base-case, implying that the base-case results may be over-estimating the benefits of selpercatinib"	Please amend as follows: "Such a preferable method might produce results that demonstrate less of a benefit for selpercatinib than observed in the base-case, implying that the base-case results **could** be over-estimating the benefits of selpercatinib **if such a preferable method exists**."	It should be clarified that the base case results would only be over-estimating the benefit of selpercatinib *if* an alternative method for adjusting for confounding exists which produces results that demonstrate less of a benefit for selpercatinib. Whether such a method exists is not known, so the wording in the EAG report should be updated to make this clear.	Not a factual inaccuracy

Issue 23 HTA database search dates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 125 Table 4.1, no date ranges were reported for the HTA database search.	Please add: **"2016–2019"** to be added to the date ranges column for HTA database.	In the Company Submission, it was specified that published information from key HTA bodies was reviewed, and a manual search was conducted for abstracts that were published between 2016 and 2019.	Amended

Issue 24 Model structure

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 129 states: "Nevertheless, the company argued that PSM and STM estimates typically converge as the data mature and prior NICE appraisals of oncology treatments indicated that the choice of a PSM or STM approach typically has a limited impact."	Please amend as follows: "Nevertheless, the company argued that PSM and STM estimates typically converge as the data mature and prior NICE appraisals of oncology treatments indicated that the choice of a PSM or STM approach typically has a limited impact. **Further to this, the Company noted that STM require strong assumptions such as a constant probability of death in the progressed disease health state. These assumptions can lead to an increased risk that the model will not accurately represent outcomes within the period covered by the clinical evidence.[4] Due to the sparsity of data in this indication, use of an STM would require the transition probabilities between states to be informed by assumptions. In comparison, data collected during the LIBRETTO-001 trial can be directly implemented in a PSM, reducing the need for strong structural assumptions."**	For transparency, the arguments made by Lilly both in favour and against and STM approach should be provided in the EAG report.	Not a factual inaccuracy

Issue 25 Population wording

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 130 states: "In addition, the company argued that clinical experts were expected to follow the same recommendation for people with squamous advanced NSCLC as for people with non-squamous advanced NSCLC."	Please amend as follows: "In addition, the company argued that clinical experts **consulted as part of a recent NICE appraisal, TA760 for selpercatinib in previously treated *RET* fusion-positive advanced NSCLC noted that the NHS would expect to follow the same recommendation for people with squamous advanced NSCLC as for people with non-squamous advanced NSCLC.[5] As such, the Committee agreed that the recommendations would apply to both squamous and non-squamous advanced NSCLC.[5]**	For transparency, the full arguments presented by Lilly at the clarification question stage should be provided. In particular, it is important to highlight that the clinical experts were consulted as part of a recent appraisal for selpercatinib in a similar indication and that the Committee concluded that the recommendation should apply to both histological subgroups, despite the prior TA also not presenting efficacy data in the squamous population.	Not a factual inaccuracy

Issue 26 Model comparator choice

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 130 states: "In addition, the company argued that patients with a positive RET status are most commonly treated with either pemetrexed with platinum-based chemotherapy or pembrolizumab plus pemetrexed with platinum-based chemotherapy, and as such, these were the only	Please amend as follows: "In addition, the company noted that **feedback received from UK clinical experts stated that** patients with a positive RET status are most commonly treated with either pemetrexed with platinum-based chemotherapy or pembrolizumab plus pemetrexed with platinum-based chemotherapy, and as such, these were the only comparators considered relevant to this	It should be highlighted that the selection of pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy as the main comparators of relevance to this is supported by multiple UK clinical experts.	Not a factual inaccuracy

comparators considered relevant to this submission." AND Page 130 states: "In response to the clarification letter, the company stated that comparator choice was informed by feedback received from expert oncologists practicing in the NHS and was supported by an RWE study to ensure only the most relevant comparators to selpercatinib in UK clinical practice were selected."	submission. **This viewpoint is in alignment with that provided by UK clinical experts as part of the recent appraisal of pralsetinib in the same indication."** **AND** "In response to the clarification letter, the company stated that comparator choice was informed by feedback received from expert oncologists practicing in the NHS, **which was in alignment with the viewpoint of clinical experts consulted as part of the recent appraisal of pralsetinib in the same indication,** and was supported by an RWE study to ensure only the most relevant comparators to selpercatinib in UK clinical practice were selected."		

Issue 27 Criteria for determining the best parametric fit

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 131 states: "The main outcomes for treatment effectiveness were PFS and OS. The company stated that the criteria considered for determining the best parametric fit were: 1) goodness-of-fit statistics (AIC and BIC); 2) assessment of visual fit to the	Please amend as follows: "The main outcomes for treatment effectiveness were PFS and OS. The company stated that the criteria considered for determining the best parametric fit were: 1) goodness-of-fit statistics (AIC and BIC); 2) assessment of visual fit to the observed KM curve; 3) clinical expert opinion regarding	The choice of survival distribution used for PFS/OS/TTD in the economic model was informed by alignment of the modelled value with external data and therefore this criteria should also be included in the EAG's list.	Not a factual inaccuracy

observed KM curve; and 3) clinical expert opinion regarding the plausibility of the long-term extrapolations of each function." Page 132 states: "Based on clinical expert opinion, the company selected the spline knot 1 model for the modelling of OS in the selpercatinib and pemetrexed plus platinum-based chemotherapy arms."	the plausibility of the long-term extrapolations of each function **and 4) alignment with external data**." "Based on clinical expert opinion **and alignment with external data**, the company selected the spline knot 1 model for the modelling of OS in the selpercatinib and pemetrexed plus platinum-based chemotherapy arms."	As noted in Section B.3.2.3 of the Company submission, selection of the survival distribution to model OS for selpercatinib in the base case analysis was informed by both clinical expert opinion and alignment with the results of a real-world evidence study (Tan *et al.* 2020)[6] evaluating OS in a population of *RET* fusion-positive NSCLC patients as well as a study in alectinib (another targeted NSCLC therapy).[7]	

Issue 28 Median OS of survival curves

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 4.5 on Page 134 states: "the median OS of the log-logistic, spline knot 2 and stratified Gompertz curves [redacted] was closest to the mean (18 months) based on expert opinion (12-24 months)".	Please amend as follows: "The median OS of the **exponentia**l, spline knot 2 and stratified and **unstratified** Gompertz curves [redacted] was closest to the mean (18 months) based on expert opinion (12-24 months)."	In Table 44 of the Company Submission, a median OS of [redacted] months was reported for the exponential, spline knot 2 and stratified and unstratified Gompertz curves.	Amended as follows: The median OS of the spline knot 2 and stratified Gompertz curves was 12.2 months while the mean of the exponential and unstratified Gompertz curves was 12.43 months. The OS of these four curves fall into the range of expected OS based on expert opinion (12-24 months).

Issue 29 Choice of OS survival distribution for selpercatinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 135 states: "Upon request for clarification, the company argued that complex curves were added 'in the interest of maximising clinical plausibility', which, according to the EAG, does not justify why standard parametric curves were insufficient for the modelling of OS."	Please amend as follows: "Upon request for clarification, the company argued that complex curves were added 'in the interest of maximising clinical plausibility, **alignment with external data in other targeted treatments in NSCLC' and assessment of diagnostic plots which the company argued showed some evidence of complex changing hazards over time.** The EAG, think this does not justify why standard parametric curves were insufficient for the modelling of OS."	In response to Clarification Question B.4 and B.5, Lilly provided smoother hazard plots requested by the EAG to explore complexity of the hazards and explained that the exponential distribution produced similarly consistent values to the spline-knot 1 model, when compared to the estimates provided by clinical experts, however, the spline-knot 1 model was ultimately selected as "it aligned closer with real-world evidence in other targeted treatments in NSCLC.[6, 7]" This additional justification should therefore be provided as it explains why a complex hazard function was selected over a standard parametric model.	Not a factual inaccuracy

Issue 30 Median versus mean post-progression TTD in LIBRETTO-001

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 136 states: "This was confirmed by the median post progression TTD in the	Please amend as follows: "This was confirmed by the **mean** post progression TTD in the LIBRETTO-001 trial, which was [redacted]."	In Table 48 of the Company Submission, it is stated that the TTD is a mean value and not a median. The statement in the EAG	Amended

LIBRETTO-001 trial, which was **********"		report should therefore be adjusted accordingly.	

Issue 31 Median PFS for pemetrexed-based therapies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 137 states: "The EAG, however identified a retrospective review of records that reports a median PFS of 19 months for patients with RET-rearranged lung cancers which were treated with pemetrexed-based therapies (like both comparators). Based on this evidence, the EAG considers the modelled effectiveness of pemetrexed plus platinum chemotherapy to be potentially underestimated, and hence the treatment effect of selpercatinib versus pemetrexed plus platinum chemotherapy overestimated."	Please amend as follows: "The EAG, however identified a retrospective review of records that reports a median PFS of 19 months for patients with RET-rearranged lung cancers which were treated with pemetrexed-based therapies (like both comparators). Based on this evidence, the EAG considers the modelled effectiveness of pemetrexed plus platinum chemotherapy to be potentially underestimated, and hence the treatment effect of selpercatinib versus pemetrexed plus platinum chemotherapy to **potentially** overestimated, **although note that this review was based on a small sample size (n=18)**. "	It should be made clear that the 'overestimation' of the treatment effect of selpercatinib versus pemetrexed plus platinum based chemotherapy is an unknown and is based on PFS estimates obtained from a small sample size.	Not a factual inaccuracy

Issue 32 Health state utility values

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 139 states: "The company justified the high utility values and small progressed disease utility decrement with the fact that patients in the SAS1 population of the LIBRETTO-001 were younger than patients in other NSCLC TAs and were mainly non-smokers."	Please amend as follows: "The company justified the high utility values and small progressed disease utility decrement with the fact that patients in the SAS1 population of the LIBRETTO-001 were younger than patients in other NSCLC TAs and were mainly non-smokers. **The company noted that the view that *RET*-fusion positive patients typically have higher utility values than patients with other forms of lung cancer was supported by feedback received from clinical experts consulted during TA760**.[8]"	It is important to note that the view that patients with *RET*-fusion positive NSCLC typically have higher utility values than the general NSCLC population is supported by UK clinical experts.	Not a factual inaccuracy

Issue 33 Health state costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 142 states: "Health state resource use estimates were based on TA654 for osimertinib (CS, Table 62), which the company considered a reasonable proxy."	Please amend as follows: "Health state resource use estimates were based on TA654 for osimertinib (CS, Table 62), which the company considered a reasonable proxy **as osimertinib represents another targeted treatment option in NSCLC**."	Justification for why health state resource use estimates from TA654 were considered a reasonable proxy was provided in Section B.3.4.2 of the Company submission. For transparency this justification should be provided in the EAG report.	Not a factual inaccuracy

Issue 34 Pembrolizumab combination therapy as a subsequent treatment options

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 143 states: "Given that the company did not include pembrolizumab combination therapy as a subsequent treatment option after selpercatinib in its economic model…"	Please amend as follows: "Given that the company did not include pembrolizumab combination therapy as a subsequent treatment option after selpercatinib in its economic model**, as it is not recommended by NICE for use in the second line setting**…"	It is important the justification provided in Section B.3.4.1 of the Company submission is added here to show that the exclusion of pembrolizumab combination therapy is in alignment with the UK clinical practice.	Not a factual inaccuracy

Issue 35 TECH-VER checklist

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 148 states: "The EAG asked to company to complete the TECH-VER checklist to support the technical verification of the economic model (Clarification Question B27)… This seems reasonable to the EAG (though the EAG is unable to verify this as the company's checklist was not provided in response to Clarification Question B27)."	Please amend as follows: "The EAG asked to company to complete the TECH-VER checklist to support the technical verification of the economic model **(Part B of Clarification Question B.26)… This seems reasonable to the EAG ~~(though the EAG is unable to verify this as the company's checklist was not provided in response to clarification question B27)~~."**	The TECH-VER checklist was provided in Appendix E of the clarification question responses in response to Part B of Clarification Question B.26. As such, the end of this sentence should be deleted.	Not a factual inaccuracy

Section 2: Data errors

Issue 1 Increased overall survival (OS) values

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.2 on Page 15 states: "…increased overall survival (OS) for selpercatinib (survival (undiscounted) increased by ***** and ***** years compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively)." AND Page 145 states: "increased OS for selpercatinib (survival (undiscounted) increased by ***** and ***** years compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively)."	Please amend as follows: Page 15: "…increased overall survival (OS) for selpercatinib (survival (undiscounted) increased by ***** and ***** years compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively)." Page 145: "increased OS for selpercatinib (survival (undiscounted) increased by ***** and ***** years compared with pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy respectively)."	As given in Table 48 and 49 of Appendix J of the Company Submission, the incremental (undiscounted) life years (LYs) gained for pembrolizumab combined therapy are ***** years, and ***** years for pemetrexed plus platinum chemotherapy. The values have therefore been incorrectly swapped for these therapies. The highlighting for these values is correct.	Amended

Issue 2 Value for iNHB^2 in the deterministic EAG base-case

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 1.19 on Page 26 reports the iNHB^2 value for the	Please amend as follows:	This value is inconsistent with the value presented in Section 6Table	Amended

deterministic EAG base-case for pemetrexed plus platinum chemotherapy to be: "[redacted]"	iNHB2 value for Deterministic EAG base-case for Pemetrexed plus platinum chemotherapy: [redacted]	6.2 of the EAG report and does not align with the probabilistic EAG base-case value provided in Table 6.2.	

Issue 3 Death or disease progression proportion in the LIBRETTO-001 trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 73 states: "Death or disease progression was reported in [redacted] of patients over a median follow-up of 21.9 months."	Please amend as follows: "Death or disease progression was reported in **29/69 (42.0%)** of patients over a median follow-up of 21.9 months."	As per Table 17 of the Company Submission, death or disease progression was reported in 42.0% of patients. This value is reported in Drilon *et al*. (2022) and therefore confidentiality marking is not required.	Amended

Issue 4 The proportion of treatment emergent adverse in the OSAS safety analysis set

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93 states: "In the OSAS, the TEAE of AST increase was reported in [redacted]patients [redacted]related to selpercatinib; [redacted]Grade [redacted]Grade 3–4 and related to selpercatinib). The TEAE of ALT increase was reported in [redacted]of OSAS patients ([redacted]related to selpercatinib; [redacted]Grade 3–4; [redacted]Grade 3-4 and	Please amend as follows: "In the OSAS, the TEAE of AST increase was reported in 36.7% patients (28.8% related to selpercatinib; 8.8% Grade 3–4; **6.3%** Grade 3–4 and related to selpercatinib). The TEAE of ALT increase was reported in 35.7% of OSAS patients (28.5% related to selpercatinib; 11.5% Grade 3–4; **9.0%** Grade 3-4 and related to selpercatinib). The majority of ALT and AST TEAEs were Grade 1 or 2.[9]"	As per page Page 91 of the Company Submission, 6.3% of TEAEs of AST increase were Grade 3–4 and related to selpercatinib and 9.0% TEAEs of ALT were Grade 3–4 and related to selpercatinib. These values are reported in Drilon *et al*. (2022) and	Amended

related to selpercatinib). The majority of ALT and AST TEAEs were Grade 1 or 2.[9]"		therefore confidentiality marking is not required.	

Issue 5 The proportion of patients suffering from treatment-emergent hypertension

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 94 states: "In the OSAS, the AE of hypertension was reported in 41% of patients (28.1% considered related to selpercatinib), with 19.6% classified as Grade 3 and 0.1% classified as Grade 4. Of patients having experienced Grade 3–4 AEs of hypertension 0.6% were considered to be related to selpercatinib. A similar proportion of NSCLC SAS patients experienced hypertension (141 [39.6%]), with 68 (19.1%) classified as Grade 3 and none as Grade 4."	Please amend as follows: "In the OSAS, the AE of hypertension was reported in 41% of patients (28.1% considered related to selpercatinib), with 19.6% classified as Grade 3 and 0.1% classified as Grade 4. Of patients having experienced Grade 3–4 AEs of hypertension **13.2%** were considered to be related to selpercatinib. A similar proportion of NSCLC SAS patients experienced hypertension (141 [39.6%]), with 68 (19.1%) classified as Grade 3 and none as Grade 4."	As per Page 92 of the Company Submission, of patients having experienced Grade 3–4 AEs of hypertension, 13.2% were considered to be related to selpercatinib.	Amended

Issue 6 Hazard ratio data reproduction from KEYNOTE-189

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 3.50, row 2 on Page 121 the OS HR (95% CrI) and PFS HR (95% CrI) appear to be	Please amend as follows: For OS – **0.49 (0.38, 0.64)**	Values present in cited work – Gandhi *et al.* (2018).	Amended. We have also amended the meta-analyses that we conducted for section

misquoted from the source literature (KEYNOTE-189).	For PFS – **0.52 (0.43, 0.64)**		3.5 that were based on these results. The conclusions do not change.

Issue 7 Sample size of the KEYNOTE-189 population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 3.50 on Page 121 states the population size of the KEYNOTE-189 trial to be "N=206"	Please amend the population size of the KEYNOTE-189 trial to "**N=616**"	Gandhi *et al.* 2018 reports that there are 206 patients in the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial and 410 patients in the pembrolizumab plus pemetrexed plus platinum chemotherapy arm of the trial and therefore the total population of KEYNOTE-189 should be amended to N=616.[10]	Amended

Issue 8 Values for subsequent treatment distributions and costs applied in the base-case analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 4.9 on Page 142 under "Selpercatinib (%)" state the values for subsequent treatment distributions and costs applied in the base-case analysis to be as follows: "55%", "45%" and "4,430"	Please amend as follows: **"56%", "44%"** and "**1,427"**	In the Company Submission and CEM, the values are those stated in the amendment. Please see Table 60 in the Company Submission for reference.	Not a factual inaccuracy. In the company's model, subsequent treatment post selpercatinib included 55% docetaxel and 45% carboplatin. The ERG assumed that the 45% carboplatin was an error by

			the company and should be 45% pemetrexed plus platinum chemotherapy as reported in the CS and the clinical validation meeting minutes. The corresponding total subsequent treatment costs are £4,430.

Issue 9 Mean weekly cycle costs for selpercatinib for progression-free state

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 142 states that for selpercatinib: "The mean weekly cycle costs per progression-free state was £74.97"	Please amend as follows: "The mean weekly cycle costs per progression-free state was **£74.79"**	In the Company Submission, the amended value is stated. Please see Table 68 of the Company Submission for reference.	Amended

Issue 10 Probabilistic base-case results for selpercatinib ICER

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 5.1 on Page 145 the incremental ICER/QALY for selpercatinib is stated to be: "36,025"	Please amend as follows: "36,078"	In the Company Submission, the amended value is stated. Please see Table 71 of the Company Submission for reference.	Not a factual inaccuracy. The ERG noted a difference between the value reported in the CS and the value in the economic model. The ERG chose to report the value from the economic model, which was 36,025.

Section 3: Confidentiality marking errors

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 45; Section 3.2	The primary outcome events threshold of the LIBRETTO-431 study and the anticipated dates associated with this threshold are commercial in confidence as per Lilly's response to the clarification questions.	"The interim analysis will be event driven and will be conducted when approximately ** events in the primary outcome, PFS by BICR, have been observed in the ITT-pembrolizumab population. It is anticipated this criterion will be met in *******, with results expected to be available from *******."	Amended
Page 47; Section 3.2.1.1	The number of patients starting on a lower dose of selpercatinib (80 mg BID) is academic in confidence.	"A total of ** patients started on a lower dose of 80 mg BID, and this was due to the Phase I 'dose finding' nature of LIBRETTO-001."	Amended
Page 48; Section 3.2.1.1; Table 3.5 AND Page 67; Section 3.2.4; Table 3.16	The number of patients in the SAS1 population is reported in Drilon *et al.* (2022) and therefore does not need to be marked as academic in confidence.	"SAS1 population **(N=69)**"	Amended
Page 48; Section 3.2.1.1	The most common reason for treatment discontinuation has not been marked as academic in confidence.	"The most common reason for treatment discontinuation was ********** (CS, Table 12)."	Amended, but could only find on p65

Page 52; Section 3.2.1.1; Table 3.7	Median follow-up for OS in the LIBRETTO-001 trial is reported in in Drilon *et al.* (2022).	"The first patient was treated on 9 May 2017. At the latest data cut-off of 15 June 2021, the median follow-up was **25.2** months for OS and 21.9 months for PFS for SAS1 (treatment-naïve) patients.[11]"	Amended
Page 57; Section 3.2.2.1; Table 3.9; rows 2 and 6 and 11	The number of patients in the integrated analysis set (second line),NSCLC Safety analysis set and the NSCLC efficacy analysis set are reported in Drilon *et al.* (2022) and therefore does not need to be marked as academic in confidence.	"**247**" and "**356**"	Amended
Page 58; Section 3.2.2.1	The number of patients in the NSCLC efficacy analysis set is reported in Drilon *et al.* (2022) and therefore does not need to be marked as academic in confidence.	"An interim analysis was conducted for **796** patients with advanced solid tumours who had enrolled in the LIBRETTO-001 trial as of a 15 June 2021 data cut-off.[9] Unless noted otherwise, the results presented and analysed in this submission are based on this data cut-off. The safety evaluable data set includes all **796** patients treated with selpercatinib as of the 15 June 2021 data cut-off."	Amended
Page 62; Section 3.2.3.1	Some of the baseline characteristics reported in Section 3.2.3.1 have been published in Drilon *et al.* (2022) and therefore academic in confidence marking is not required.	"The median age of patients with in the SAS1 population was **63** (range: **23–92**) years and a greater proportion of participants were female (**62.3%;** Table 3.12). The majority (**69.6%**) of patients were white, with a high proportion of patients identified as Asian (**18.8%**). Most participants (**69.6%**) reported never smoking." AND	Amended

<table>
<tr><td></td><td></td><td>“Most patients (98.6%) had metastatic disease at enrolment, with 23.2% exhibiting CNS metastases at baseline. In addition, most patients were diagnosed with Stage IV or greater disease (91.3%).”</td><td></td></tr>
<tr><td>Page 63; Section 3.2.3.1; Table 3.12</td><td>The values denoting median age, sex, race, baseline ECOG, and smoking history of the SAS1 subgroup have been published in Drilon et al. (2022) and therefore academic in confidence marking is not required.</td><td>
<table>
<tr><th>Characteristics</th><th>SAS1 (treatment-naïve), N=69</th></tr>
<tr><td>Median (range)</td><td>63.0 (23-92)</td></tr>
<tr><td>Male</td><td>26 (37.7)</td></tr>
<tr><td>Female</td><td>43 (62.3)</td></tr>
<tr><td>White</td><td>48 (69.6)</td></tr>
<tr><td>Black</td><td>4 (5.8)</td></tr>
<tr><td>Asian</td><td>13 (18.8)</td></tr>
<tr><td>Other/Missing</td><td>4 (5.8)</td></tr>
<tr><td>Never smoked</td><td>48 (69.6)</td></tr>
<tr><td>Former smoker</td><td>19 (27.5)</td></tr>
<tr><td>Current smoker</td><td>2 (2.9)</td></tr>
</table>
</td><td>Amended</td></tr>
<tr><td>Page 64; Section 3.2.3.1; Table 3.13</td><td>The values denoting CNS metastases at baseline by investigator and RET fusion partner of the SAS1 subgroup have been published in Drilon et al. (2022) and therefore academic in confidence marking is not required.</td><td>
<table>
<tr><th>Characteristics</th><th>SAS1 (treatment-naïve), N=69</th></tr>
<tr><td colspan="2">CNS metastases at baseline by investigator, n (%)</td></tr>
<tr><td>Yes</td><td>16 (23.2)</td></tr>
<tr><td>No</td><td>53 (76.8)</td></tr>
<tr><td colspan="2">RET fusion partner, n (%)</td></tr>
<tr><td>KIF5B</td><td>48 (69.6)</td></tr>
<tr><td>CCDC6</td><td>10 (14.5)</td></tr>
</table>
</td><td>Amended</td></tr>
</table>

		NCOA4 **1 (1.4)**	
Page 65; Section 3.2.3.1; Table 3.15	The number of patients treated in the SAS1 subgroup and the percentage of those with treatment ongoing is not academic in confidence.	Please remove the academic in confidence marking from the values: “69” and “32 (46.4) in Table 3.15	Amended
Page 68; Section 3.2.5; Table 3.17; study question 6A	The number of patients continuing treatment at the latest data cut-off in the SAS1 population of the LIBRETTO-001 trial is not academic in confidence and therefore the confidentiality marking can be removed.	“Yes. Out of the 69 subjects enrolled in the treatment-naïve cohort of LIBRETTO-001, a high proportion of patients (**46.4%**) were continuing treatment at the latest data cut-off.[9]”	Amended
Page 71; Section 3.2.6.1.1	Some of the data reported here have been published in Drilon *et al.* (2022) and therefore do not require academic in confidence marking.	“The median OS in the SAS1 trial population was ********** at the 15 June 2021 data cut-off, with the majority of patients (**49; 71%**) remaining alive at a median follow-up of **25.20** months. At 12 months, the OS rate was **92.7%** (**95% CI: 83.3–96.9**) and at 24 months was **69.3% (95% CI: 55.2–79.7**), providing preliminary evidence to support that selpercatinib will result in an extension to patients’ lives (Table 3.19).”	Amended
Page 73; Section 3.2.6.1.1	The anticipated dates associated with the next LIBRETTO-001 data cut-off are commercial in confidence.	“Lilly responded by stating that, “At this current time, no data from a later data cut-off from the LIBRETTO-001 trial are available. The next data cut-off from the LIBRETTO-001 trial is anticipated to occur in *******, with results expected to become available in ********”. The EAG is satisfied with this response.”	Amended

Page 73; Section 3.2.6.1.1	The median duration of PFS in the SAS1 population is reported in Drilon *et al.* (2022) and therefore does need to be marked as academic in confidence. The value has been updated to align with the significant figures reported in Drilon *et al.* (2022). This amendment should be made throughout the EAG report.	"As of the 15 June 2021 data cut-off, the majority (37; 53.6%) of patients were alive and without documented PD, with a median duration of PFS of **22.0** months (95% CI: 13.8–NE) months."	Amended
Page 73; Section 3.2.6.1.1	The number of patients experiencing death or disease progression in the SAS1 population is reported in Drilon *et al.* (2022) and therefore does need to be marked as academic in confidence.	"Death or disease progression was reported in **32/69 (46.4%)** of patients over a median follow-up of 21.9 months."	Amended
Page 73; Section 3.2.6.1.1	The probability of patients being progression-free at 12 months in the SAS1 population is reported in Drilon *et al.* (2022) therefore does need to be marked as academic in confidence.	By KM estimates, the probability of patients being progression-free at 6- and 12- months was [redacted] and **70.6% (95% CI: 57.8–80.2),** respectively, by Independent Review Committee (IRC) assessment	Amended

Page 73; Section 3.2.6.1.1; Table 3.20; row 3	The value for disease progression is reported in Drilon *et al.* (2022) and therefore does need to be marked as academic in confidence.	"**29 (42.0)**"	Amended
Page 74; Section 3.2.6.1.1; Table 3.2; row 13 and 14	Median PFS for the SAS1 population is reported in Drilon *et al.* (2022) and therefore does need to be marked as academic in confidence. Please note, the value has been updated to reflect the number of significant figures in the publication. This amendment should be made in all relevant places in the report.	"**22.0**"	Amended
Page 74; Section 3.2.6.2.1; Table 3.20; rows 18 and 19	The rates and 95% CIs of PFS in the SAS1 population of the LIBRETTO-001 trial at ≥6 and ≥12 months were reported in Drilon *et al.* (2022).	"**70.6 (57.8–80.2)** **41.6 (26.8–55.8)**"	Amended
Page 76; Section 3.2.6.3.	The proportion of patients assessed to have a BOR of stable disease, partial response and progressive disease were reported in Drilon *et al.* (2022). The number of significant	"Based on BOR, **9**% of patients were assessed to have stable disease, whilst the majority were assessed to have a partial response (**78%**). Only **three** patients (**4%**) were assessed to have PD as BOR."	Amended

	figures can be updated in line with those reported in the publication.		
Page 76; Section 3.2.6.3.1.	Some results for tumour diameter change in the SAS1 population of the LIBRETTO-001 trial have been reported in Drilon *et al.* (2022).	"The individual patients' responses to selpercatinib treatment in terms of percentage decrease in tumour size from baseline, as per RECIST v1.1, are illustrated in Figure 3.3, demonstrating that at the data cut-off, tumour diameter had decreased in **all of the 69** patients, decreasing by more than 30% (i.e., at least a partial response was achieved) in all but [redacted] patients."	Amended
Page 76; Section 3.2.6.3.1; Table 3.21; rows 3–7	BOR data for patients in the SAS-1 population of the LIBRETTO-001 trial were reported in Drilon *et al.* (2022). The number of significant figures can be updated in line with those reported in the publication.	"**4 (6)** **54 (78)** **6 (9)** **3 (4)** **2 (3)**"	Amended
Page 82; Section 3.2.7.5.1.	The proportion of patients in the SAS1 population of the LIBRETTO-001 trial with investigator-assessed brain metastases at baseline has been reported in Drilon *et al.* (2022).	"A total of **16 (23.2%)** of the 69 treatment-naïve patients had Investigator assessed brain metastases at baseline."	Amended
Page 86; Section 3.2.7.5.1.	CNS ORR subgroup results for patients with measurable CNS lesions are academic in confidence as per the Company Submission.	"These data are supported by the subgroup analysis performed in the SAS1 (treatment-naïve NSCLC) trial population of the LIBRETTO-001 trial which found that patients with measurable CNS lesions had a CNS ORR of [redacted]."	Amended

<table>
<tr>
<td>Page 87; Section 3.2.7.5.1; Table 3.25, row 1</td>
<td>The number of patients in the SAS1 population of the LIBRETTO-001 trial has been reported in Drilon et al. (2022).</td>
<td>SAS1 population (N=69)
N=69</td>
<td>Amended</td>
</tr>
<tr>
<td>Page 87; Section 3.2.7.5.1.</td>
<td>Baseline characteristics of patients in the SAS1 population of the LIBRETTO-001 trial are academic in confidence as per Lilly's response to clarification questions.</td>
<td>"The characteristics of patients in the survey are broadly aligned with the baseline characteristics of patients in the SAS1 population of the LIBRETTO-001 trial: median age (64.7 versus [redacted] years, respectively) and the proportion of patients who were not Hispanic or Latino (99% versus [redacted], respectively) were similar."</td>
<td>Amended</td>
</tr>
<tr>
<td>Page 88; Section 3.2.6; Table 3.26</td>
<td>Data for the median age, sex and ECOG score in the SAS1 population in LIBRETTO-001 were reported in Drilon et al. (2022).</td>
<td>
<table>
<tr><th>Characteristics</th><th>NSCLC DSP Wave IV, N=74</th><th>SAS1 (LIBRETTO-001). N=69</th></tr>
<tr><td colspan="3">Age, years</td></tr>
<tr><td>Median</td><td>64.7</td><td>63.0</td></tr>
<tr><td colspan="3">Sex, n (%)</td></tr>
<tr><td>Male</td><td>39 (53)</td><td>26 (37.7)</td></tr>
<tr><td>Female</td><td>35 (47)</td><td>43 (62.3)</td></tr>
<tr><td colspan="3">Race/ethnicity, n (%)</td></tr>
<tr><td>Hispanic/Latino</td><td>1 (1)</td><td>[redacted]</td></tr>
<tr><td>Not Hispanic or Latino</td><td>73 (99)</td><td>[redacted]</td></tr>
<tr><td>Missing</td><td>0 (0)</td><td>[redacted]</td></tr>
<tr><td colspan="3">ECOG score at advanced diagnosis, n (%)</td></tr>
<tr><td>0</td><td>11 (15)</td><td>25 (36.2)</td></tr>
<tr><td>1</td><td>52 (70)</td><td>40 (58.0)</td></tr>
</table>
</td>
<td>Amended</td>
</tr>
</table>

		2 | 7 (9) | 4 (5.8) 3 | 1 (1) | 0 (0.0) 4 | 3 (4) | 0 (0.0) **Current disease stage, n (%)** IV or greater | 74 (100) | [redacted] **Investigator reported history of metastatic disease, n (%)** Yes | NR | [redacted] No | NR | [redacted] **Molecular assay type, n (%)** NGS with tumour tissue | 10 (37) | [redacted] PCR on tumour | 6 (22) | [redacted] FISH on tumour | 15 (56) | [redacted] NGS on plasma/blood | 0 (0) | [redacted] Nano string technology | 0 (0) | [redacted]	
Page 89; Section 3.2.8.1.	The reported adverse event and dose reduction/interruption data are academic in confidence as per the CS.	"Dose reductions were required in [redacted] patients in the OSAS and [redacted] patients in the RET fusion-positive NSCLC SAS, with the most common reason being adverse events (AEs; [redacted] [41%] and [redacted], respectively) (Table 3.29). Dose interruptions occurred in [redacted] of the OSAS and [redacted] of the NSCLC SAS, with the most common reason being AEs ([redacted] and [redacted], respectively). There were [redacted] and [redacted] dose increases in the OSAS and NSCLC SAS, respectively."	Amended

<table>
<tr>
<td>Page 90; Section 3.2.8; Table 3.29</td>
<td>The number of patients in the OSAS population, the proportion who experienced dose reduction for an AE, and values for dose interruption for AE for the SAS population were reported in Drilon et al. (2022). The number of significant figures can be changed in line with publication.</td>
<td>
<table>
<tr><th></th><th>SAS (RET fusion-positive NSCLC; N=356)</th><th>OSAS (overall population; N=796)</th></tr>
<tr><td colspan="3">Dose reduction, n (%)</td></tr>
<tr><td>Any</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>For AE</td><td>[redacted]</td><td>[redacted] (41)</td></tr>
<tr><td>For other reason</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="3">Dose interruption, n (%)</td></tr>
<tr><td>Any</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>For AE</td><td>245 (68.8)</td><td>510 (64.1)</td></tr>
<tr><td>For other reason</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td colspan="3">Dose increase, n (%)</td></tr>
<tr><td>Any</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Intra-patient escalation[a]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Re-escalation[b]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Other reason</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Amended</td>
</tr>
<tr>
<td>Page 91; Section 3.2.8.1.2.</td>
<td>Some safety data presented here are not academic in confidence as they were reported in Drilon et al. (2022).</td>
<td>In the OSAS, 95% of AEs were considered to be related to selpercatinib but the majority were deemed to be of low severity, with 38.6% classed as Grade 3 or Grade 4 (Table 3.30). A similar pattern was observable in the NSCLC SAS. Permanent discontinuation of selpercatinib due to AEs were infrequent (3.1%) in the OSAS, with no predominant pattern among the individual AEs reported. One fatal treatment emergent adverse event (TEAE) within 28 days of last dose was attributed to selpercatinib in the OSAS, and zero deaths related to selpercatinib occurred in the NSCLC SAS.

A high proportion of patients in the OSAS (99.9%) experienced at least one TEAE during treatment. The most common TEAEs, defined as</td>
<td>Amended</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td>occurring in 15% of patients or more, in the OSAS were: oedema (48.5%), diarrhoea (47.0%), fatigue (45.9%), dry mouth (43.2%), hypertension (41%), aspartate aminotransferase (AST) increase (36.7%), alanine transaminase (ALT) increase (35.7%), constipation (32.8%), abdominal pain (33.7%), rash (32.8%) and nausea (31.2%).”</td><td></td></tr>
<tr><td>Page 91; Section 3.2.8; Table 3.30</td><td>Summary data of safety trends in the OSAS population were reported in Drilon et al. (2022).</td><td>
<table>
<tr><th></th><th>SAS (RET fusion-positive NSCLC; N=356)</th><th>OSAS (overall population; N=796)</th></tr>
<tr><td colspan="3">Any TEAE, n (%)</td></tr>
<tr><td>All</td><td>356 (100.0)</td><td>795 (99.9)</td></tr>
<tr><td>Related to selpercatinib</td><td>341 (95.8)</td><td>756 (95.0)</td></tr>
<tr><td colspan="3">Grade 3 or 4 TEAE, n (%)</td></tr>
<tr><td>All</td><td>263 (73.9)</td><td>572 (71.9)</td></tr>
<tr><td>Related to selpercatinib</td><td>143 (40.2)</td><td>307 (38.6)</td></tr>
<tr><td colspan="3">TEAE leading to treatment discontinuation, n (%)</td></tr>
<tr><td>All</td><td>34 (9.6)</td><td>64 (8.0)</td></tr>
<tr><td>Related to selpercatinib</td><td>[redacted]</td><td>25 (3.1)</td></tr>
<tr><td colspan="3">TE-SAE, n (%)</td></tr>
<tr><td>All</td><td>[redacted]</td><td>353 (44.3)</td></tr>
<tr><td>Related to selpercatinib</td><td>[redacted]</td><td>87 (10.9)</td></tr>
<tr><td colspan="3">Fatal TEAE</td></tr>
</table>
</td><td>Amended</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>All</td><td>[redacted]</td><td>45 (5.7)</td></tr>
<tr><td>Related to selpercatinib</td><td>[redacted]</td><td>1 (0.1)</td></tr>
<tr><td colspan="3"></td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Page 92; Section 3.2.8.1.2; Table 3.31.</td>
<td>Data for the maximum severity incidence for the OSAS population are not academic in confidence as they were reported reported in Drilon et al. (2022) and/or the Company Submission.</td>
<td>
<table>
<tr><th rowspan="2">Preferred term</th><th colspan="4">Maximum severity incidence, n (%)</th></tr>
<tr><th colspan="2">SAS (RET fusion-positive NSCLC; N=356)</th><th colspan="2">OSAS (overall population; N=796)</th></tr>
<tr><th>Any Grade</th><th>Grade ≥3</th><th>Any Grade</th><th>Grade ≥3</th></tr>
<tr><td>Oedema</td><td>178 (50.0)</td><td>2 (0.6)</td><td>386 (48.5)</td><td>6 (0.8)</td></tr>
<tr><td>Diarrhoea</td><td>184 (51.7)</td><td>15 (4.2)</td><td>374 (47.0)</td><td>40 (5.0)</td></tr>
<tr><td>Fatigue</td><td>153 (43.0)</td><td>8 (2.2)</td><td>365 (45.9)</td><td>25 (3.1)</td></tr>
<tr><td>Dry mouth</td><td>163 (45.8)</td><td>0 (0.0)</td><td>344 (43.2)</td><td>0 (0.0)</td></tr>
<tr><td>Hypertension (AESI)</td><td>141 (39.6)</td><td>68 (19.1)</td><td>326 (41.0)</td><td>157 (19.7)</td></tr>
<tr><td>AST increased</td><td>149 (41.9)</td><td>37 (10.4)</td><td>292 (36.7)</td><td>70 (8.8)</td></tr>
<tr><td>ALT increased</td><td>147 (41.3)</td><td>[redacted]</td><td>284 (35.7)</td><td>91 (11.4)</td></tr>
</table>
</td>
<td>Amended</td>
</tr>
</table>

Abdominal pain	101 (28.4)	5 (1.4)	**268 (33.7)**	**20 (2.5)**		
Constipation	96 (27.0)	5 (1.4)	**261 (32.8)**	**6 (0.8)**		
Rash	130 (36.5)	4 (1.1)	**261 (32.8)**	**5 (0.6)**		
Nausea	112 (31.5)	4 (1.1)	**248 (31.2)**	**9 (1.1)**		
Blood creatinine increased	92 (25.8)	10 (2.8)	**227 (28.5)**	**15 (1.9)**		
Headache	94 (26.4)	3 (0.8)	**220 (27.6)**	**11 (1.4)**		
Cough	87 (24.4)	0 (0.0)	**184 (23.1)**	**0 (0.0)**		
Dyspnoea	84 (23.6)	16 (4.5)	**179 (22.5)**	**25 (3.1)**		
Vomiting	78 (21.9)	4 (1.1)	**178 (22.4)**	**14 (1.8)**		
ECG QT prolongation (AESI)	74 (20.8)	21 (5.9)	**168 (21.1)**	**38 (4.8)**		
Arthralgia	[redacted]	[redacted]	**165 (20.7)**	**2 (0.3)**		
Back pain	[redacted]	[redacted]	**153 (19.2)**	**12 (1.5)**		
Dizziness	[redacted]	[redacted]	**152 (19.1)**	**2 (0.3)**		

		Decrease appetite	[redacted]	[redacted]	**150 (18.8)**	**3 (0.4)**	
		Pyrexia	79 (22.2)	1 (0.3)	**135 (17.0)**	**1 (0.1)**	
		Urinary tract infection	70 (19.7)	8 (2.2)	**135 (17.0)**	**12 (1.5)**	
		Thrombocytopenia	74 (20.8)	20 (5.6)	**123 (15.5)**	**24 (3.0)**	
		Dry skin	[redacted]	[redacted]	**122 (15.3)**	**0 (0.0)**	
		Hypocalcaemia	[redacted]	[redacted]	**121 (15.2)**	**22 (2.8)**	
Pages 92–93; Section 3.2.8.1.3.	These safety data were reported in Drilon *et al.* (2022).	"In the OSAS, Grade 3 or 4 TEAEs were reported in **572** (**71.9%**) patients, irrespective of relatedness to study drug (Table 3.32). The most common Grade 3–4 events were hypertension (**19.7%**), ALT increase (**11.4%**), and AST increase (**8.8%**) in the OSAS. Despite the relatively high level of Grade 3–4 TEAEs observed in the OSAS, only a small proportion (**307 [38.6%]**) were considered by the Investigator to be related to selpercatinib. In the NSCLC SAS, **263** (**73.9%**) patients experienced Grade 3–4 TEAEs, irrespective of relatedness to selpercatinib (Table 3.32). A smaller proportion (**143 [40.2%]**) were considered by the Investigator to be related to selpercatinib. Common TEAEs mirrored the OSAS analysis set"					Amended

Page 93; Section 3.2.8.1.3; Table 3.32	Data for the OSAS population are not academic in confidence as they were reported in Drilon *et al.* (2022).	**Preferred term**	**SAS (*RET* fusion-positive NSCLC; N = 356)**		**OSAS (overall population; N=796)**		Amended
			Any	**Related to selpercatinib**	**Any**	**Related to selpercatinib**	
		One or more Grade 3–4 AEs	263 (73.9)	143 (40.2)	**572 (71.9)**	**307 (38.6)**	
		Hypertension	68 (19.1)	49 (13.8)	**157 (19.7)**	**105 (13.2)**	
		ALT increased	53 (14.9)	41 (11.5)	**91 (11.4)**	**72 (9.0)**	
		AST increased	37 (10.4)	24 (6.7)	**70 (8.8)**	**50 (6.3)**	
		Lymphopenia	[redacted]	[redacted]	**41 (5.2)**	**NR**	
		Diarrhoea	15 (4.2)	8 (2.2)	**40 (5.0)**	**16 (2.0)**	
		ECG QT prolonged	21 (5.9)	14 (3.9)	**38 (4.8)**	**27 (3.4)**	
		Pneumonia	[redacted]	[redacted]	**34 (4.3)**	**NR**	
		Fatigue	8 (2.2)	3 (0.8)	**25 (3.1)**	**17 (2.1)**	
		Dyspnoea	16 (4.5)	12 (3.6)	**25 (3.1)**	**14 (2.0)**	
		Thrombocytopenia	20 (5.6)	[redacted]	**24 (3.0)**	**0**	

		<table><tr><td>Anaemia</td><td>[redacted]</td><td>[redacted]</td><td>23 (2.9)</td><td>9 (1.3)</td></tr><tr><td>Hypocalcaemia</td><td>[redacted]</td><td>[redacted]</td><td>22 (2.8)</td><td>2 (0.3)</td></tr><tr><td>Pleural effusion</td><td>[redacted]</td><td>[redacted]</td><td>21 (2.6)</td><td>2 (0.3)</td></tr></table>	
Page 93, Section 3.2.8.1.4.	These safety data are not academic in confidence as they were reported in Drilon *et al.* (2022) and/or the Company Submission.	"In the OSAS, the TEAE of AST increase was reported in **36.7%** patients (**28.8%** related to selpercatinib; **8.8%** Grade **3–4; 1.1%** Grade 3–4 and related to selpercatinib). The TEAE of ALT increase was reported in **35.7%** of OSAS patients (**28.5%** related to selpercatinib; **11.5%** Grade 3–4; **1.5%** Grade 3-4 and related to selpercatinib)."	Amended
Page 94; Section 3.2.8.1.4.	These safety data are not academic in confidence as per the Company Submission.	"In the OSAS, the AE of hypertension was reported in **41%** of patients (**28.1%** considered related to selpercatinib), with **19.6%** classified as Grade 3 and 0.1% classified as Grade 4. Of patients having experienced Grade 3–4 AEs of hypertension **0.6%** were considered to be related to selpercatinib. A similar proportion of NSCLC SAS patients experienced hypertension (**141 [39.6%]),** with **68 (19.1%)** classified as Grade 3 and **none** as Grade 4.[12] Whilst hypertension was frequently reported, it can be managed easily and therefore did not result in substantial dose reductions or treatment interruptions. A minority of OSAS patients required dose interruption ([redacted]) and/or reduction (**1.3%**). [redacted] patient discontinued therapy due to an AE of hypertension. Moreover, of the **796** OSAS patients, [redacted] of patients had a reported chronic history of hypertension and [redacted] did not. The frequency of reported hypertension AEs was similar between these patients despite the difference in medical history."	Amended

Page 94; Section 3.2.8.1.4.	These safety data were reported in Drilon *et al.* (2022).	"Any grade ECG QT prolongation was reported for **168** patients (**21.1%**), with **130 (16.3%)** considered related to selpercatinib in the OSAS. The majority of events were Grade 1 or Grade 2."	Amended
Page 9; Section 3.2.8.1.4.	The number of patients who had an AE of QT interval corrected for heart rate using QTcF prolongation that was deemed serious is academic in confidence as per the Company Submission.	"[redacted]had an AE of QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation that was deemed serious."	Amended
Page 95; Section 3.2.8.1.4.	The proportion of patients who permanently discontinued selpercatinib due to TEAEs was reported in Drilon *et al.* (2022).	"As a result, permanent discontinuation of selpercatinib due to TEAEs were infrequent (**8%**), meaning patients could consistently benefit from the highly efficacious anti-tumour activity of selpercatinib."	Amended
Page 96; Section 3.3	The primary outcome events threshold and the anticipated dates associated with this threshold are commercial in confidence as per the Lilly's response to the clarification questions.	"Lilly responded by stating that, "*The interim analysis will be event driven and will be conducted when approximately [redacted] events in the primary outcome, PFS by BICR, have been observed in the ITT-pembrolizumab population. It is anticipated this criterion will be met in [redacted], with results expected to be available from [redacted].*"	Amended

Page 100; Section 3.3.1; Table 3.35	All LIBRETTO-001 data presented in this table was reported in Drilon *et al.* (2022).	All data in the "LIBRETTO-001, SAS1" row of Table 3.35 can have its AiC highlighting removed.	Amended
Page 101; Section 3.3.1; Table 3.36	Baseline characteristics for the SAS1 population of the LIBRETTO-001 were reported in Drilon *et al.* (2022).	Academic in confidence marking can be removed from the following data in row 1 of Table 3.36 for the LIBRETTO-001 SAS1 population: • **'69'** • **'100'** • **'25'** • **'36.2'** • **'40'** • **'58.0'** • **'4'** • **'5.8'**	Amended
Page 112; Section 3.4.1	Percentages of patients who had 'never smoked' in the selpercatinib cohort and the propensity-score-matched pemetrexed plus platinum chemotherapy plus placebo cohort are academic in confidence as per the Company Submission.	"Also, the populations were sufficiently different to make sufficient overlap impossible for some variables (e.g., those who "never smoked" comprised [redacted] of the selpercatinib cohort but only [redacted] of the propensity-score-matched pemetrexed plus platinum chemotherapy plus placebo cohort)."	Amended

<table>
<tr><td>Page 113; Section 3.4.1</td><td>The numbers of patients who were removed from the SAS1 dataset for reasons of ECOG performance status = 2 and missing stage data are academic in confidence as per the Company Submission.</td><td>“In addition to the 142 patients excluded from the KEYNOTE-189 cohort, five patients were removed from the SAS1 dataset (n=69) to facilitate propensity matching. The reasons were ECOG performance status = 2 ([redacted]) and missing stage data ([redacted]).”</td><td>Amended</td></tr>
<tr><td>Page 113; Section 3.4.1</td><td>Data reporting the number of patients with an ECOG score of 2 in the SAS1 population of KEYNOTE-189 is academic in confidence as per the Company Submission.</td><td>“Lilly responded by stating that, “Lilly can confirm that the decision on patient eligibility was made pre-hoc before the matching/weighting approaches were attempted. The reason for this pre-hoc decision on exclusion from the SAS1 database being made was that the KEYNOTE-189 study had an inclusion criterion to enrol only patients with an ECOG performance score of 0 or 1. Therefore, it would not be possible to find patients from the KEYNOTE-189 trial who matched the [redacted] patients with an ECOG score of 2 in the SAS-1 population of the LIBRETTO-001 trial.”[13]</td><td>Amended</td></tr>
<tr><td>Page 114; Section 3.4.2</td><td>The data for PFS for selpercatinib in LIBRETTO-001 were reported in Drilon et al. (2022).</td><td>“This study showed a PFS of 19 months (95% CI 12–not reached), very similar to that for selpercatinib in LIBRETTO-001 (21.95 months (95% CI: 13.8–NE) months).</td><td>Amended</td></tr>
<tr><td>Page 129; Section 4.2.3; Table 4.4</td><td>The value for the percentage of females in the SAS1 population of LIBRETTO-001 is reported in the latest Drilon (2022) publication.</td><td><table><tr><th>Model parameter</th><th>Value</th></tr><tr><td>Mean age (years)</td><td>[redacted]</td></tr><tr><td>Female (%)</td><td>62.3</td></tr><tr><td>Mean weight (kg)</td><td>[redacted]</td></tr></table></td><td>Amended</td></tr>
</table>

<table>
<tr>
<td>Page 129 and 135; Section 3.2.6</td>
<td>The value for progressed disease is reported in Drilon et al. (2022) publication.</td>
<td>“42% had progressed and [redacted] had died”</td>
<td>Amended</td>
</tr>
<tr>
<td>Page 138; Section 4.2.8; Table 4.6</td>
<td>The utility values for the Company Submission base-case and Company Submission scenario analysis are not published and should be marked as academic in confidence in line with the Company Submission.</td>
<td>
<table>
<tr><th></th><th>Health state</th><th>Utility value</th></tr>
<tr><td rowspan="2">CS base-case</td><td>PF</td><td>[redacted]</td></tr>
<tr><td>PD</td><td>[redacted]</td></tr>
<tr><td rowspan="2">CS scenario analysis</td><td>PF</td><td>[redacted]</td></tr>
<tr><td>PD</td><td>[redacted]</td></tr>
</table>
</td>
<td>Amended</td>
</tr>
</table>

Section 4: Typographical errors

Issue 1 Statement on LIBRETTO-001 as a single arm trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 3.3 on Page 46 states: “N/A – LIBRETTO-001 is a single am trial”	Please amend as follows: “N/A – LIBRETTO-001 is a single **arm** trial”	This is a typographical error.	Amended

Issue 2 Correction of ‘analyses’ spelling

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 3.10 on Page 59 states: “Patients treated during the Phase I portion of the study who meet the Phase II eligibility criteria for one of the Phase II cohorts were included as part of the evaluable patients for that cohort for efficacy analyse.”	Please amend as follows: “Patients treated during the Phase I portion of the study who meet the Phase II eligibility criteria for one of the Phase II cohorts were included as part of the evaluable patients for that cohort for efficacy **analyses**.”	This is a typographical error.	Amended

Issue 3 ECOG/WHO performance status sub-column formatting

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 3.36 on Page 101, the “ECOG/WHO performance status” column does not include the “2” score sub-column due to a minor formatting error which causes it to appear in the “AJCC stage” column.	Please amend as follows: This formatting should be adjusted as appropriate so that ECOG/WHO performance status 0, 1 and 2 are captured under the relevant column heading.	This is a minor formatting error.	Amended

Issue 4 Incorrect footnote

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The footnote for Table 3.36 on Page 101 states that the table is "Based on Table 32, Appendices […]"	Please amend this footnote follows: Alter this table footnote to read "Based on Table 33, Appendices […]"	This is a typographical error.	Amended

Issue 5 Incorrect description of the type of models assessed in the NMA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 114 states: "For the NMA, both randomised effects and fixed effects models were assessed for all outcomes and the model which best fitted the data were used; in the base-case a random effects model was selected for all outcomes"	Please amend as follows: "For the NMA, both **random** effects and fixed effects models were assessed for all outcomes and the model which best fitted the data were used; in the base-case a random effects model was selected for all outcomes"	This is a typographical error – Section B.2.8.3 of the Company Submission states that both random effects and fixed effects models were assessed for all outcomes in the NMA. This amendment should be applied to all relevant places in the EAG report.	Amended

Issue 6 Corrected tornado diagrams clarification response number

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 147 states: "The company provided corrected tornado diagrams, see clarification response 20 and 21"	Please amend as follows: "The company provided corrected tornado diagrams, see clarification response **B27 (Figure 20 and Figure 21**)"	In the clarification responses, corrected tornado diagrams were provided in Figure 20 and Figure 21.	Amended

References

1. MHRA. Selpercatinib (Retsevmo) 40 mg hard capsules. SmPC. Available at: https://mhraproducts4853.blob.core.windows.net/docs/8f5ea7915fcb7efbcd55b16ff524f79dcf3de751. (Accessed 03/11/22).
2. NICE. Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta11012. [Last accessed: 14.10.22]
3. Eli Lilly and Company Limited. Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]. Document B. Company evidence submission. Single technology appraisal (STA): Eli Lilly and Company Limited, 2022.
4. NICE. Pemetrexed for the first-line treatment of non-small-cell lung cancer [TA181]. Available at: https://www.nice.org.uk/Guidance/TA181 [Accessed: 18.10.2022].
5. National Institute for Health and Care Excellence. Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer (TA760). Available at: https://www.nice.org.uk/guidance/ta760. Accessed: 14/01/2022., 2022.
6. Tan AC, Seet AOL, Lai GGY, et al. Molecular Characterization and Clinical Outcomes in RET-Rearranged NSCLC. J Thorac Oncol 2020;15:1928-1934.
7. ClinicalTrials.Gov Study of Pemetrexed+Platinum Chemotherapy With or Without Pembrolizumab (MK-3475) in Participants With First Line Metastatic Nonsquamous Non-small Cell Lung Cancer (MK-3475-189/KEYNOTE-189). Available at: https://clinicaltrials.gov/ct2/show/results/NCT02578680. Accessed: 10/08/22., 2022.
8. Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer. [TA760]. Available at: https://www.nice.org.uk/guidance/ta760. (Accessed 14.10.22).
9. Eli Lilly and Company. Data on file. LIBRETTO-001 Clinical Study Report: Eli Lilly and Company, 2021.
10. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. New England journal of medicine 2018;378:2078-2092.
11. Drilon A, Subbiah V, Gautschi O, et al. Selpercatinib in patients with RET fusion-positive non-small-cell lung cancer: updated safety and efficacy from the registrational LIBRETTO-001 phase I/II trial. Journal of Clinical Oncology 2022;Online ahead of print.
12. Eli Lilly and Company. Data on file. Clinical health technology assessment toolkit: assessment of clinical efficacy and safety for LY3527723: Eli Lilly and Company, 2020.
13. Eli Lilly and Company Limited. Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]. Clarification responses: Eli Lilly and Company Limited, 2022.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **23 January 2023**. 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 during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1. About you

Your name	XXXXXXXXXXXXXXX
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Eli Lilly and Company Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2. Key issues

Key issue	Does this response contain new evidence, data or analyses? (Yes/No)	Response
Key issue 1: Population: uncertainty as to whether includes squamous histology for which no evidence has been provided.	No	Eli Lilly and Company (Lilly) acknowledge the concerns of the External Assessment Group (EAG) that no direct evidence is available for the clinical efficacy of selpercatinib in squamous rearranged during transfection (*RET*) fusion-positive non-small cell lung cancer (NSCLC). However, as noted in response to Clarification Question A.8, the proportion of *RET* fusion-positive NSCLC tumours exhibiting squamous histology is small. This is evidenced by a retrospective observational study by Hess *et al.,* (2021), which showed that patients with metastatic *RET* fusion-positive NSCLC were significantly more likely to be of a non-squamous histology than the general NSCLC population.[1] As such, whilst not an exclusion criterion of the LIBRETTO-001 trial, the relative rarity of squamous *RET* fusion-positive NSCLC resulted in no patients exhibiting squamous histology being included in the Supplemental Analysis Set 1 (SAS1).[2] Despite this, Lilly are seeking a broad recommendation for selpercatinib in the first-line setting, unrestricted by squamous histology. This is in line with NICE Committee conclusions in a recent technology appraisal for selpercatinib in previously treated *RET* fusion-positive advanced NSCLC (TA760).[3] The Committee in that appraisal noted the lack of distinction made between squamous and non-squamous histological subgroups in the selpercatinib marketing authorisation, and the Cancer Drugs Fund clinical lead stated that NHS prescribing patterns would likely be the same across both squamous and non-squamous patient groups, due in part to the small patient subpopulation with squamous disease.[3]

		Therefore, in consideration of the data paucity challenges inherently associated with rare disease indications, Lilly recommend that a decision to extend the recommendation to a squamous population be left up to the discretion and judgement of the Committee.
Key issue 2: Comparators: mismatch to NICE scope and NICE guideline, which might undermine the validity of any effectiveness or cost-effectiveness estimates.	No	Whilst acknowledging that not all of the comparators listed in the final scope are presented in the economic model, Lilly maintain that the comparators that are included are the only comparators relevant to the target population in UK clinical practice. This is because, as noted in response to Clarification Question A.9, comparator choice was informed by feedback received from expert oncologists practicing in the NHS to ensure that only treatment options most relevant to UK clinical practice were selected for consideration as comparators to selpercatinib. During a consultation led by Lilly, an expert oncologist identified single agent immunotherapy as the "least likely" treatment option that *RET* fusion-positive patients would receive in UK clinical practice.[4] This may be due to a lower efficacy of immunotherapies alone in patients with *RET* fusion NSCLC as compared to other NSCLC patient populations, which was noted by a second expert oncologist.[4] The limited efficacy of mono-immunotherapy in these patients is supported by the conclusions of a real-world evidence study conducted by Offin *et al*. in 2019, which found median PFS in patients with *RET* fusion-positive NSCLC treated with mono-immunotherapy to be just 3.4 months (95% CI: 2.1 to 5.6 months).[5] The authors concluded that *RET* fusion-positive lung cancers may be less likely to be highly responsive to immunotherapy as compared with other cancers, and noted that this was reflected in the overall poor outcomes observed. In addition to this, the expert oncologist consulted by Lilly emphasised that UK clinicians typically avoid the use of mono-immunotherapies as first line options in *RET* fusion-positive patients due to the associated toxicities that can occur if a tyrosine kinase inhibitor (TKI) is subsequently provided in the second line.[4] This is consistent with reported rates of selpercatinib-related hypersensitivity reactions, which are considerably more frequent in patients who have been previously treated with an immune checkpoint inhibitor.[6] In alignment with these conclusions of limited efficacy and a potentially limiting safety profile of mono-immunotherapies in the patient population of interest, a representative of the Royal College of Pathologists consulted during the Technical Engagement process stated that "*At the moment, patients must endure chemotherapy/immunotherapy/both before being able to access targeted treatment; these alternative options are associated with more side effects than targeted treatment. In addition, there is good evidence to show that these patients do not derive benefit*

		from immunotherapy" (Technical Engagement Papers, Page 255).[7] In the place of mono-immunotherapy options, the expert oncologists stated that *RET* fusion-positive patients in UK clinical practice typically receive either pemetrexed with platinum-based chemotherapy or pembrolizumab in combination with pemetrexed plus platinum chemotherapy (pembrolizumab combination therapy) first line.[4] In particular, the expert feedback highlighted that because *RET* fusion-positive patients are typically younger with a higher proportion of non-smokers than the wider NSCLC population, they are most commonly treated with pembrolizumab combination therapy, as evidence has shown this to be the most effective treatment option in these patients.[4] A recent real-world evidence study supports the higher efficacy and safety of pembrolizumab combination therapy in patients with better performance statuses (Eastern Cooperative Oncology Group [ECOG] performance status 0–1) than in those with those with poor performance statuses (ECOG performance status 2–3), and this may underlie the prescribing trend outlined by the clinical expert.[8] Based on these considerations, the comparators chosen in the base case were pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy. This feedback, and the subsequent comparator selection, is aligned with that received from clinical experts consulted as part of the recent evaluation of pralsetinib in the same indication (TA812).[9] As such, Lilly maintain that pemetrexed plus platinum chemotherapy and pembrolizumab combination therapy are the only relevant comparators to selpercatinib in this indication.
Key issue 3: Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice.	Yes	As noted by the EAG, selpercatinib is not currently provided first-line to patients with treatment-naïve *RET* fusion-positive advanced NSCLC, so there is no real-world evidence available for what would constitute subsequent treatment in this case. Moreover, due to the relatively low number of SAS1 patients (treatment-naïve subset) in the LIBRETTO-001 trial as compared to wider safety sets, the sample size of patients receiving subsequent therapies in this group is limited ([redacted]). For these reasons, the distribution of subsequent therapies used in the Company Submission base case was informed by prior technology appraisals, as outlined in Section B.3.4.1 in Document B. However, Lilly acknowledge that the subsequent treatments informed by expert clinician input, which represents the EAG preference for informing this distribution, may be more reflective of clinical practice in the UK. As such, the base case approach has been updated to consider the subsequent therapy distributions provided by expert

		clinicians, although Lilly do note that pembrolizumab and atezolizumab, both of which are included at 2.5% of the subsequent treatment distribution as per the expert clinician input, are not reimbursed in the NHS. As presented in Table 11, this amendment had a minimal impact on incremental cost-effectiveness ratio (ICER) with respect to both selpercatinib versus pembrolizumab combination therapy and selpercatinib versus pemetrexed and platinum chemotherapy. Furthermore, Lilly acknowledge that the subsequent treatment distributions of patients in the LIBRETTO-001 trial is informed by a small patient number, and as such may not be wholly representative of current treatment of *RET* fusion-positive NSCLC in the NHS. In addition, the cohort contains patients in the LIBRETTO-001 trial who went on to receive anti-cancer therapies second-line, as data on the receipt of best supportive care (BSC) was not routinely collected during the trial. To address the concerns of the EAG that discrepancies between the subsequent therapy distribution of the LIBRETTO-001 trial and typical NHS clinical practice may bias the results of the cost-effectiveness analysis towards selpercatinib with respect to overall survival (OS) post disease progression, scenario analyses have been provided in the updated economic model in which the subsequent treatment distributions are informed by the available LIBRETTO-001 data (as presented in response to Clarification Question A.20; Appendix A Table 32). Lilly acknowledge the difficultly in interpreting the original tables provided in the Company clarification response and as such have provided simplified tables in response to Key Issue 17 below, where additional information on how to interpret these data is also presented. In line with the EAG's preference, two scenario analyses based on the LIBRETTO-001 data have been provided: the first scenario analysis incorporates all subsequent treatments reported in the LIBRETTO-001 trial, regardless of whether they are reimbursed in the NHS, whilst the second scenario analysis omits subsequent treatments used in the LIBRETTO-001 trial which are not reimbursed in the NHS. The results of these scenario analyses are presented in Table 25 in Appendix I and indicate that any mismatch between the LIBRETTO-001-informed distribution and the distribution informed by clinical experts (which informs the updated base case) is minimally impactful on the overall results. Switching the subsequent therapy distribution to align with the LIBRETTO-001-informed distribution resulted in an ICER change of −3.9% when treatments not reimbursed in the UK were excluded, showing the more relevant of the two scenarios to have a negligible impact on the overall cost-effectiveness results. Whilst the change in the ICER from the base case was greater for selpercatinib versus pembrolizumab combination therapy in this scenario, the resultant ICER of £3,265/QALY

		still fell well below a modified cost-effectiveness threshold of £36,000/QALY. Lilly cautions the Committee on the relevance of these scenario analyses given the small number of post-progression observations that inform them and the limited relevance of some of the subsequent treatments to the NHS. However, these scenario analyses demonstrate the economic model to be robust to the subsequent treatment distribution utilised.
Key issue 4: Lack of comparative evidence in the correct population, which might mean treatment effect of selpercatinib overestimated and ICERs underestimated.	No	Lilly acknowledge the concerns of the EAG regarding the lack of comparative evidence on the characteristics of the UK target population. However, at outlined in response to Clarification Question A.18, *RET* fusion-positive NSCLC is a rare condition, with an upper estimate of 2% of all lung cancer cases exhibiting *RET* fusion.[10] As such, data specific to this patient population were unavailable from clinical trials in comparator therapies. As detailed in response to Clarification Question A.23, in the absence of comparative evidence in the correct population, adjustments were made for differences in the baseline characteristics between the SAS1 population and the trial used to generate the pseudo control arm. Since the pemetrexed and platinum chemotherapy arm of the KEYNOTE-189 trial was the only arm with available IPD, it was utilised to generate the pseudo control arm. IPD were selected for use in preference to population data for several reasons. First, the insufficient data on outcomes would mean that use of a population adjusted method, such as a matching-adjusted indirect comparison (MAIC) described in NICE DSU 18, would introduce greater bias to the analyses and cause methodological difficulties. Second, aggregate adjustments methods account for population 'moments' only, whereas IPD adjustment methods match patients based on individual baseline characteristics.[11] Patient matching is essential for producing a representative ITC because patients in the treatment-naïve *RET* fusion-positive set (SAS1) of the LIBRETTO-001 trial are younger, healthier and with a higher proportion of non-smokers as compared with a broader NSCLC patient cohort.[1] Furthermore, the large imbalances in certain baseline characteristics caused by *RET* fusion-positive status means that use of a population adjusted method would greatly reduce the size of the LIBRETTO-001 dataset (n=69), resulting in increased uncertainty in the results of the ITC. Finally, an observational study by Tierney *et al.*, (2020) comparing trial and meta-analyses results from 18 systematic reviews in cancer found that aggregate adjustment methods were more unreliable when utilised for studies with relatively small population sizes or small numbers of recorded events, with the hazard ratios (HRs) derived from aggregate adjustment versus IPD adjustment methods converging as the information size (population size or number of events) increased.[12] Therefore, since the SAS1 population of the

		LIBRETTO-001 trial had a sample size of n=69, use of aggregate adjustment methods were not considered appropriate for this analysis. With respect to the population included in these analyses, Lilly would like to highlight that evidence from Hess *et al*. 2021 shows no statistically significant difference in either PFS (HR: 1.24; 95% CI: 0.86–1.78; p=0.25) or OS (HR: 1.52; 95% CI: 0.95–2.43; p=0.08) between patients with and without *RET* fusions treated with standard therapies, including pemetrexed plus platinum chemotherapy, following adjustments for baseline covariates.[1] Whilst acknowledging the limitations of this study, such as potential unmeasured confounding, the lack of statistically significant difference in adjusted survival outcomes by *RET* status supports that *RET* status is not inherently prognostic. As such, there is no evidence to suggest that the effectiveness of pemetrexed would be expected to differ in *RET* fusion-positive patients, provided appropriate adjustments for baseline covariates are performed. This conclusion of *RET* fusion status not representing a prognostic factor is supported by the analyses presented in previous NICE appraisals of RET fusion-positive indications, TA760 and TA812, neither of which adjusted for *RET* fusion-positive status in their NMAs.[3, 9] For these reasons, Lilly maintain that the results of the ITC are unlikely to be biased in favour of selpercatinib and that the use of adjusted data from the pemetrexed and platinum chemotherapy arm of the KEYNOTE-189 trial remains appropriate, particularly in light of the limitations of the comparator evidence base in this rare indication.
Key issue 5: Applicability: there is no information on the characteristics of the UK target population, meaning that comparability between trial and target population cannot be assumed	No	Lilly acknowledge the concerns of the EAG regarding the lack of comparative evidence on the characteristics of the UK target population. However, as outlined in response to Key Issue 4 above, *RET* fusion-positive NSCLC is a rare condition, with an upper estimate of 2% of all lung cancer cases exhibiting *RET* fusion.[10] As such, data specific to this patient population in the UK are sparse. Despite this, in response to Clarification Question A.18, Lilly provided data on the characteristics of 74 UK patients with treatment-naïve *RET* fusion-positive advanced NSCLC obtained from a Lilly-commissioned survey. The results of the survey found the demographic and disease characteristics of the UK target population for potential treatment effect modifiers were broadly generalisable to the baseline characteristics of the SAS1 population of the LIBRETTO-001 trial. For example, the median ages of patients were similar: 64.7 and [redacted] years, for the survey and SAS1 population, respectively. Additionally, in both the survey and the SAS1

		population, the most common ECOG score was 1 (70% versus [redacted], respectively). A full comparison of the baseline demographic and disease characteristics between the SAS1 population and the treatment-naïve, *RET* fusion-positive survey participants based in the UK (N=74) is provided in Table 12, Appendix A. Similarities between these populations indicate that any potential treatment modifying effects observed in the SAS1 population are likely to be reflective of the UK target population. Furthermore, whilst data on the proportion of patients with CNS metastases were not obtained from the survey results, UK clinical experts did not identify any major discrepancies between the baseline characteristics of the SAS1 population and patients in UK clinical practice, providing support that any potential treatment modifying effects relating to CNS metastases would also be comparable to the UK population.[4] In the context of a rare disease, these data are a valuable reference point for the baseline characteristics of these patients in UK clinical practice and provide supportive evidence that the baseline characteristics of the SAS1 population of the LIBRETTO-001 trial are broadly generalisable to the UK target population.
Key issue 6: Adverse events: there are no specific adverse event data for the treatment naïve sub-set (SAS1 dataset) in LIBRETTO-001, or the equivalent subset of the LIBRETTO-321.	Yes	Lilly wish to clarify that specific adverse event data for the treatment-naïve subset of patients (SAS1, N=69) in the LIBRETTO-001 trial were used in the Company Submission to inform the base case of the cost-effectiveness model. These data are presented in full in Appendix B. In addition, Lilly note that safety data from the SAS1 population specifically have been made available to the European Medicines Agency and published as part of a Public Assessment Report.[13] Critically, the report concludes: "*The overall safety profile of selpercatinib in Treatment-Naïve Patients is consistent with that of the Overall Safety Population. The updated results provided in this analysis show the safety profile of selpercatinib is consistent with that reported previously, even with longer duration of treatment*." Furthermore, no new adverse drug reactions or adverse events of special interest have been reported since initial authorisation.[13] However, for completeness, Lilly present an additional scenario analysis in which safety data from the NSCLC Safety Analysis Set (SAS; N=356, which included all patients with documented RET fusion-positive NSCLC, including all 69 patients in the SAS1 population) are considered, rather than data derived from the SAS1 population only. The use of a larger sample size permits inclusion of all safety data from the SAS1 population of interest whilst simultaneously increasing the chance of identifying less common adverse events that are more likely to have been missed in an analysis of the smaller SAS1 population alone. The results of this scenario analysis are presented in Appendix I; Table 25 and do not alter the conclusions of cost-effectiveness previously

		drawn.
Key issue 7: ITC: choice of trial data (KEYNOTE-189) might have biased comparison with all comparators.	No	As detailed in response to Clarification Question A.23, the use of the pemetrexed and platinum chemotherapy arm of the KEYNOTE-189 trial as the source of comparator data was predicated on it being the only comparable trial found for which individual patient data (IPD) were available. Importantly, no potential comparator trials reporting data for a patient population in which *RET* fusion status is determined were identified. As discussed further in response to Key Issue 4, while recent evidence supports that *RET* fusion status itself is not a prognostic factor, differences in the baseline characteristics between patients with RET fusion-positive NSCLC as compared to those with *RET* fusion-negative NSCLC mean that appropriate adjustments for baseline covariates must be performed in order to produce robust and meaningful comparative results.[1] As such, patient matching is essential in producing a representative ITC. The use of an IPD method rather than aggregate data allows for patient matching based on baseline characteristics, rather than just accounting for population 'moments', and is more robust given the available sample size of N=69 from the LIBRETTO-001 trial (see response to Key Issue 4 above for further details).[11, 12] With respect to the KEYNOTE-189 trial specifically, the baseline characteristics of its enrolled patients treated with pemetrexed plus platinum chemotherapy were well-matched to the patients in analogous treatment arms of other trials included in the NMA (see Appendix C). Notably, median age and ECOG/WHO score were comparable across pemetrexed and platinum chemotherapy treatment arms of included studies (see Appendix C; Table 15). Additionally, median PFS and OS values were consistent across the pemetrexed and platinum chemotherapy treatments arms of included studies (see Table 16 and Table 17 in Appendix C for PFS and OS, respectively). As such, it is not expected that the necessary use of the pemetrexed and platinum chemotherapy arm of the KEYNOTE-189 trial to inform the ITC will have biased the outcome of the ITC relative to the other trials detailed in the EAG report. However, scenario analyses which may address the concerns of the EAG with respect to the potential bias introduced by selecting KEYNOTE-189 to inform the pseudo-comparator arm are presented in response to Key Issue 9 below.
Key issue 8:	Yes	As outlined in response to Clarification Question A.22, in line with NICE TSD17, multiple methods were

ITC: methods of adjustment for confounding might have biased comparison with all comparators.		explored for adjusting for confounding in the NMA including genetic matching, propensity score weighting (PSW) using a generalised boosted model, and PSW using a logistic regression model. Guidance provided in NICE TSD17 informed the adjustment techniques.[14] The results of these adjustment techniques explored are provided in response to Clarification Question A.22. In addition to the aforementioned methods, a targeted minimum loss-based estimation (TMLE) was explored as a potential adjustment method to address the concerns of the EAG. The methodology and results of the TLME method have been provided below. **TMLE** The TMLE was explored to simultaneously model matched covariates from the pemetrexed plus platinum chemotherapy arm and selpercatinib arm. Non-parametric log-rank test and Cox regression models were performed on the adjusted data to obtain significance tests for the treatment effect and estimate hazard ratios (HR) and confidence intervals (CI) for selpercatinib versus the pseudo-control arm. The results of the TMLE are presented in Table 3 below. **Table 3: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (TMLE)**

Endpoint	HR (95% CI)	p-value
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Abbreviations: CI: confidence interval; OS: overall survival; PFS, progression-free survival; TMLE: targeted minimum loss-based estimation.

The KM curves for PFS and OS following TMLE adjustment are provided in Figure 1.

Figure 1: Kaplan-Meier charts for PFS and OS for selpercatinib and pemetrexed plus platinum chemotherapy pseudo-control arm in treatment-naïve NSCLC patients following TMLE

		 **Abbreviations**: NSCLC: non-small cell lung cancer; OS: overall survival; PFS, progression-free survival; TMLE: targeted minimum loss-based estimation. The results for OS HR following TMLE were consistent with other adjustments techniques explored. However, the HRs for PFS were found to be considerably different (see Table 4). Approximately 22 months of follow-up data are available for selpercatinib from the LIBRETTO-001 trial, however only 14 months of follow-up data are captured in the Kaplan-Meier curves produced following TMLE adjustment. As a result, it is evident that a considerable quantity of data on longer-term follow-up was not captured in the Kaplan-Meier curves produced following TMLE due to the methodological limitations of the approach. In addition, the TMLE method simultaneously models the covariates in the two study arms being matched and estimates predicted cumulative hazard rates for the two study arms after adjustment for covariates. TMLE is a data mining technique and may require a lot of data to accurately model the covariates, but only 22 events for

		PFS and 20 events for OS were observed in the SAS1 population of the LIBRETTO-001 trial. Due to the limited event data, TMLE likely will not have had sufficient information to fit a survival model with covariates accurately. The results of the TMLE method are therefore associated with significant uncertainty. Finally, the TMLE method also produced overly optimistic PFS outcomes for pemetrexed plus platinum chemotherapy patients, with a median PFS of approximately [redacted] months. This value is almost double the median PFS observed up to a median follow-up of 46.3 months for the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial (4.9 months, as shown in Table 4) and therefore lacks external validity.[15] Additionally, of the clinical trials identified in the clinical SLR (see Section B.2.1 of the Company submission) that assessed pemetrexed plus platinum chemotherapy, all except one reported a median PFS of less than 9 months, and the single outlier with a median PFS above 9 months was associated with large confidence intervals (Appendix C; Table 16). Similarly, in the 15 clinical trials assessing pemetrexed plus platinum chemotherapy identified in the clinical SLR, a median PFS of approximately 5–6 months was typically observed. These data provide further evidence that the TMLE method produced overly optimistic PFS outcomes for the pemetrexed plus platinum chemotherapy arm which lacked external validity. The OS outcomes generated by the TMLE method were equally optimistic for pemetrexed plus platinum chemotherapy patients, with a median OS of beyond [redacted] months (see Figure 1). In comparison, the median OS observed for patients treated with pemetrexed plus platinum chemotherapy in the KEYNOTE-189 trial did not exceed 12 months over a median follow-up of 46.3 months.[15] This value from the KEYNOTE-189 trial is more closely aligned with the modelled curves for OS in the submitted economic approach, which produced a median OS of approximately [redacted] months (Section B.3.2.3 of the Company submission). Additionally, in the clinical trials assessing pemetrexed plus platinum chemotherapy identified in the clinical SLR for which median OS was estimable, median OS was typically estimated to be approximately 14–15 months (Appendix C; Table 17). These data provide evidence that the TMLE method produced overly optimistic outcomes for the pemetrexed plus platinum chemotherapy arms for both OS and PFS, which lacked external validity. Due to a combination of the high levels of uncertainty associated with the TMLE method, owing to it being unable to capture an additional 8 months of trial data, and the lack of clinical plausibility of the pemetrexed plus platinum chemotherapy PFS and OS estimates, TMLE was not considered an appropriate method to estimate treatment effects in the indirect treatment comparison (ITC). Consequently, Lilly do not present any further

analyses using these data as they are not robust enough to do so, but hope that the presentation of these data will reassure the Committee that the results of the TMLE analysis are not suitable for decision making, and alleviate the concerns of the EAG that alternative methods may have led to more accurate treatment effect estimates for inclusion in the economic model.

As outlined in response to Clarification Question A.22, a PSM approach to adjust for confounding was ultimately utilised in the ITC as the results were associated with the highest external validity; the modelled median PFS and OS were most closely aligned to those observed in the KEYNOTE-189 trial for the pemetrexed plus platinum chemotherapy arm (Table 4). This result is externally valid since, as outlined in response to Key Issue 5 above, patients in the SAS1 population of the LIBRETTO-001 trial were typically younger and healthier than the advanced NSCLC more generally. As a result, the mean age and number of non-smokers for the pemetrexed plus platinum chemotherapy arm of the KEYNOTE-189 trial were anticipated to be artificially reduced in the adjustment process, thus resulting in increased mPFS and mOS for this population. While RET fusion status could not be accounted for due to a lack of reporting in comparator trials, recent evidence showing that *RET* status does not represent a prognostic marker suggests the impact of this lack of adjustment would not be meaningfully impactful.[1] Moreover, the choice of which variables to feature in the ITC was made following a robust systematic literature review and consultation with clinical experts as stated in the response to Clarification Question A.24.

Table 4: Comparison of the mPFS and mOS generated via the different adjustment methods to the observed values from KEYNOTE-189 for the pemetrexed plus platinum chemotherapy arm

Adjustment method	mPFS (months)	mOS (months)
PSM	[redacted]	[redacted]
Genetic matching	[redacted]	[redacted]
PSW using generalised booster model	[redacted]	[redacted]
PSW using logistic regression	[redacted]	[redacted]
TMLE	[redacted]	[redacted]
KEYNOTE-189 (observed)[15]	4.9	10.6

Abbreviations: mPFS: median PFS; mOS: median OS; PSM: propensity score matching; PSW: propensity; TMLE: target minimum

		loss-based estimation; NR: not reached.
Key issue 9: NMA: heterogeneity in trials to inform pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy.	Yes	Lilly acknowledge that differences exist in the baseline characteristics featured in the studies included in the network meta-analysis (NMA). These differing characteristics include age, sex and ethnicity, but also extend to the publication year of the study in question. As outlined in Section B.2.8.3 of Document B, when running the NMAs, use of fixed-effects (FE) or random-effects (RE) was considered. In addition, RE with informative priors were explored to evaluate better model fit statistics. The differences in the deviance information criterion (DIC) values between FE and RE were within the range of ±5 points, so model selection could not be made according to DIC. Furthermore, the addition of informative priors did not improve model fit statistics and caused issues in convergence and autocorrelation. As such, results from the random-effects model with non-informative priors were considered as the base-case to account for the effects of between-study heterogeneity. Overall, the results of the heterogeneity tests confirmed that no baseline characteristics represented significant sources of heterogeneity, and thus the analysis was carried out without further adjustment, such as in the form of a meta-regression. Despite this, it is acknowledged that unquantifiable heterogeneity may be present within these groups. **Re-analysis of heterogeneity** To address concerns regarding heterogeneity within the network, the EAG performed a meta-analysis of three trials (KEYNOTE-021, KEYNOTE-189, KEYNOTE-189 Japan), comparing pembrolizumab combination therapy versus pemetrexed plus platinum chemotherapy, which highlighted the above heterogeneity in ethnicity but also likely differences in *RET* fusion status between trials. It is important to note that while this meta-analysis is a valuable addition to the Company Submission, the version presented in the EAG report (associated relative treatment effect estimates presented in Table 3.50 on Page 121) used input data from the KEYNOTE-189 and KEYNOTE-021 trials that do not align with the input data used in the Company-submitted analyses. The Company-submitted analyses used input data from the latest publications, as presented in Tables 34, 35 and 36 of Appendix D.3.1 of the Company submission for ORR, PFS and OS, respectively. For clarity, Table 3.50 of the EAG report has been updated in Appendix D; Table 18 below to present the NMA input data used to inform the Company submission alongside their respective sources. Lilly acknowledge that the study ID labelling in these tables, which noted the primary publication (from which the EAG sourced the input data) as opposed to the exact publication from which the latest input data were derived,

may not have been clear. As such, the related publications for the trials relevant to this analysis (KEYNOTE-189, KEYNOTE-189 Japan and KEYNOTE-021) are summarised in Appendix D; Table 19, with the publication from which the relevant NMA input data were obtained marked in bold.

Lilly have repeated the meta-analysis performed by the EAG using the correct input data for both KEYNOTE-189 and KEYNOTE-021, along with the data that the EAG used for KEYNOTE-189 Japan which remains unchanged in this re-analysis.[15-17] The revised results are presented in Figure 2 (OS) and Figure 3 (PFS).

Figure 2: Revised meta-analysis of the three trials comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for OS

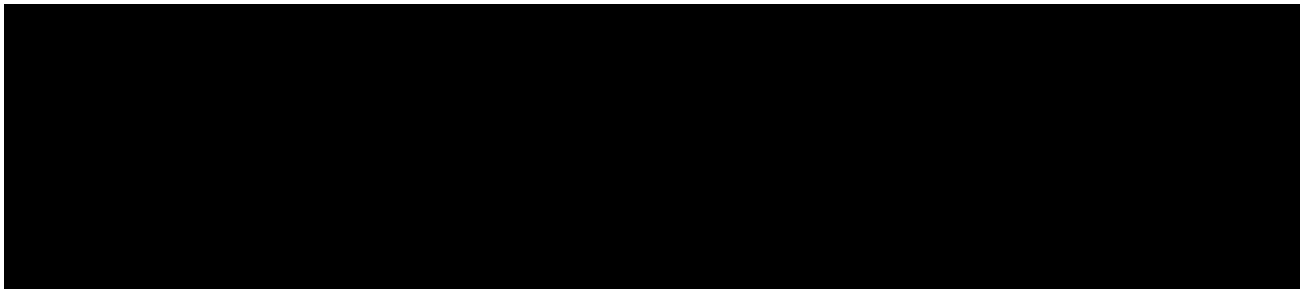
Abbreviations: CI: confidence interval; df: degrees of freedom; HR: hazard ratio; IV: inverse variance.
Source: Awad *et al.* (2021).[16] Gray *et al.* (2021).[15] Horinouchi *et al.* (2021).[17]

Figure 3: Revised meta-analysis of the three trials comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for PFS

		 **Abbreviations**: CI: confidence interval; df: degrees of freedom; HR: hazard ratio; IV: inverse variance. **Source**: Awad *et al.* (2021).[16] Gray *et al.* (2021).[15] Horinouchi *et al.* (2021).[17] **Exclusion of KEYNOTE-189 Japan** Lilly acknowledge that patients with NSCLC from Asian countries may have different baseline characteristics from those in Europe or North America.[18] In turn, this could affect patient prognosis and the effectiveness of certain treatment approaches, with notable differences in the rate of *EGFR*, *KRAS*, and *BRAF* mutations between Asian and Caucasian patient cohort. This may result in heterogeneity.[19, 20] To address this possibility, and in alignment with the EAG approach, additional analyses have been performed in which data from this trial have been removed. Results are presented in Figure 4 (OS) and Figure 5 (PFS) and show that median HR values remain well aligned for both PFS and OS upon exclusion of the KEYNOTE-189 Japan study from the pooled analysis. **Figure 4: Revised meta-analysis comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for OS, with KEYNOTE-189 Japan removed**

Abbreviations: CI: confidence interval; df: degrees of freedom; HR: hazard ratio; IV: inverse variance.
Source: Awad *et al.* (2021).[16] Gray *et al.* (2021).[15] Horinouchi *et al.* (2021).[17]

Figure 5: Revised meta-analysis comparing pembrolizumab plus pemetrexed plus platinum versus pemetrexed plus platinum for PFS, with KEYNOTE-189 Japan removed



Abbreviations: CI: confidence interval; df: degrees of freedom; HR: hazard ratio; IV: inverse variance.
Source: Awad *et al.* (2021).[16] Gray *et al.* (2021).[15] Horinouchi *et al.* (2021).[17]

The revised meta-analyses indicate a lack of meaningful heterogeneity, with statistical testing yielding an I^2 of 0% for all analyses, including those with KEYNOTE-189 Japan trial data removed. While it should be considered that this may be impacted by the statistical powering of these analyses, as noted in section 3.5 of the EAG report, this result indicates that total variability within the analyses is likely to be minimally impacted by heterogeneity.

Pooled data from these trials have been re-analysed to provide further context, using a limited network for the comparison to pembrolizumab, as compared to that detailed in Section B.2.8.3 of the Company Submission.

The updated results of this analysis, adapted from Table 3.48 of the EAG report, are presented in Table 5 (OS) and Table 6 (PFS).

Table 5: Revised relative treatment effect estimates expressed as HRs versus pembrolizumab plus pemetrexed and platinum chemotherapy (with 95% CrI) for overall survival (OS), random effects model

Treatment	Median HR (95% CrI) of selpercatinib versus comparators
Selpercatinib (original network)	[redacted]
Selpercatinib (LIBRETTO-001, KEYNOTE-021 and KEYNOTE-189 studies)	[redacted]
Selpercatinib (LIBRETTO-001, KEYNOTE-021, KEYNOTE-189 and KEYNOTE-189 Japan studies)	[redacted]

Abbreviations: CrI: credible interval; HR: hazard ratio.

Table 6: Revised relative treatment effect estimates expressed as HRs versus pembrolizumab plus pemetrexed and platinum chemotherapy (with 95% CrI) for progression free survival (PFS), random effects model

Treatment	Median HR (95% CrI) of selpercatinib versus comparators
Selpercatinib (original network)	[redacted]
Selpercatinib (LIBRETTO-001, KEYNOTE-021 and KEYNOTE-189 studies)	[redacted]
Selpercatinib (LIBRETTO-001, KEYNOTE-021, KEYNOTE-189 and KEYNOTE-189 Japan studies)	[redacted]

Abbreviations: CrI: credible interval; HR: hazard ratio.

The updated values for both OS and PFS treatment effect estimates expressed as HRs are consistent with the original values presented in the Company Submission (original network), regardless of whether KEYNOTE-189 Japan is included or omitted from the analysis. For both OS and PFS, the CrI is subject to a slight narrowing relative to the full network, which aligns with the homogeneity of the KEYNOTE studies. Slight changes (±0.01) in the estimates are within the expected range of variability for the HR estimate given that input data from the

		published studies are reported to two decimal places. With respect to *RET* fusion status, it is deemed unlikely that this would markedly contribute to heterogeneity between the studies included in the NMA and the LIBRETTO-001 trial. While patients with *RET* fusion-positive cancers may have better outcomes compared to the *RET* wildtype population, this is likely a product of a higher likelihood of these patients being younger and reporting a non-smoker status. As outlined elsewhere in this response document, there is robust evidence to suggest that when baseline covariates are suitably adjusted, there are no significant differences in either overall survival or progression-free survival based on *RET* fusion status.[1] This study is benefitted by its large sample size of patients, thus providing robust evidence that *RET* fusion status does not represent a prognostic marker.[1] This is also consistent with the recent NICE technology appraisal on pralsetinib (TA812) for treating *RET* fusion-positive advanced NSCLC, in which *RET* wildtype patient population data was used in its associated NMA.[9] Based on these additional analyses and the available real-world evidence, it is not expected that considerable heterogeneity has been included in these analyses and thus that the results represent robust and reliable estimates of the relative efficacy of selpercatinib versus a key comparator in UK clinical practice, pembrolizumab combination therapy.
Key issue 10: No NMA or comparative analysis was carried out for adverse events, preventing a rigorous assessment of benefits and harms	Yes	Lilly acknowledge that no NMA or comparative analysis was performed to assess the incidence of adverse events associated with selpercatinib and its comparators. However, it is noted that the economic model considers single safety events, which would mean safety NMAs to inform the economic analysis would need to be performed on single safety endpoints at a time. The limited number of data points per outcome would have produced NMA results associated with such uncertainty as to be insufficiently robust and informative for use in the model. Making use of adverse event summary outcomes, such as serious adverse events (SAEs), to inform comparative analyses may have avoided this issue, but considerable heterogeneity exists in the grouped safety data collected from clinical trials in relevant comparators, meaning that considerable uncertainty would have been introduced to a safety NMA. For example, SAEs were reported up to 28 days after the last dose of the intervention in the LIBRETTO-001 trial, whereas SAEs were reported up to 90 days after the last treatment dose in the KEYNOTE-189 trial, preventing a robust direct comparison.[21, 22] For this reason, it is not anticipated that

		safety NMAs, of either single or grouped endpoints, would have been able to provide results sufficiently robust for consideration in the model. In addition, Lilly note that the LIBRETTO-001 trial was powered based on its efficacy outcomes, and therefore a comparative analysis of safety data for selpercatinib versus relevant comparators based on the underpowered safety data from LIBRETTO-001 would not be statistically suitable. As such, Lilly maintain that the approach to considering adverse events presented in the Company Submission is appropriate and a comparative analysis has not been presented. However, in line with the preference of the EAG, a scenario analysis has been performed in the updated economic model in which AEs occurring at a frequency greater than or equal to 2% in any trial arm were considered. The results of this scenario analysis are presented in Appendix I; Table 25 and show that the results of the economic model are robust to the method of reporting adverse event data, with negligible changes observed as compared with the updated base case values.
Key issue 11: Lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties in the extrapolation period.	No	As laid out in the response to Clarification Question B.1, Lilly maintain that while a state transition model (STM) approach may encompass additional health states, it is not evident that this is required to model advanced NSCLC accurately. In support of this, prior NICE submissions in the NSCLC disease setting demonstrate a strong preference towards the employment of a partitioned survival model (PSM), with previous EAGs and NICE Committees expressing no concerns with this approach.[3, 9, 23, 24] In addition, the use of an STM would rely on several strong assumptions with respect to the state transition probabilities implemented, given that these data are not available from the LIBRETTO-001 trial. Such assumptions would be considerably impactful within the model and no clear approach to externally validating these assumptions is available. In particular, the method by which the outcomes of a STM could be used to verify the plausibility of the extrapolations employed within the PSM is unclear. Therefore, Lilly maintain that the employment of a PSM is appropriate and does not intend to present an STM.
Key issue 12: Immaturity of the	No	Lilly acknowledge that the maturity of the data obtained from the LIBRETTO-001 trial to date should be considered in the interpretation of the Company's economic model. However, it is important to note that the current interim analysis (15th June 2021) data are highly promising from a clinical perspective and show a

data obtained from the LIBRETTO-001 trial for OS and PFS, adding substantial uncertainty to the extrapolated survival data in the economic model

consistent trend of maintaining or improving PFS and OS estimates from LIBRETTO-001 compared to previous data-cuts, as shown in Table 7. It is important to note that recruitment for the NSCLC cohorts stopped in [redacted], and therefore it is likely that further data cuts from LIBRETTO-001 will only serve to validate the current estimates from the latest data-cut (June 2021) presented in the Company's submission.

Table 7: Progression-free survival and overall survival result from current and previous data-cuts for *RET* fusion-positive NSCLC (SAS1) – LIBRETTO-001

	17th June 2019 (original MAA)	16th December 2019 (additional 6 months follow-up)	30th March 2020 (additional 9.5 months follow-up)	15th June 2021 (additional 24 months follow-up)
N	[redacted]	[redacted]	[redacted]	[redacted]
No. of eligible patients[a]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]	[redacted]	[redacted]
Rate of progression-free survival (%)				
≥6 months	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival (months)				
Median	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Rate (%) of overall survival				
≥12 months	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

		[a]Eligible patients include all patients in the analysis set who have the opportunity to be followed for at least 6 months from the first dose of selpercatinib. Note: + = Censored Observation. **Abbreviations**: CI: confidence interval; N: number of patients in the analysis population; NE: not estimable; No.: number; NSCLC: non-small cell lung cancer; *RET*: rearranged during transfection; SAS: Supplemental Analysis Set. Further data-cuts will be available over the course of [redacted], with a data lock planned in [redacted] from LIBRETTO-001 and results available in [redacted]. Results from an interim-cut from the LIBRETTO-431 trial are also anticipated in [redacted]. It is important to note that the date for the interim-cut from LIBRETTO-431 is event-driven based on the number of PFS events, therefore no meaningful OS data are expected to be available from this trial at this interim-cut. As shown in Table 7, further data cuts from LIBRETTO-001 show consistent results for PFS and OS and therefore, Lilly urge the Committee to consider the value of recommending selpercatinib through the Cancer Drugs Fund (CDF) versus routine commissioning, given that it is likely that further data-cuts will only serve to validate the trend and consistency in PFS and OS results already seen. As *RET* fusion-positive NSCLC is a therapeutic area of considerable unmet need, treatment-naïve patients could greatly benefit from a targeted oral treatment with improved tolerability over relevant systemic therapies while data maturity concerns are resolved. Indeed, the provision of a targeted treatment would bring the standard-of-care for this patient population in line with that available for patients with NSCLC characterised by other known oncogenic mutations. Additionally, the NMA demonstrated that based on available data, selpercatinib is likely to be superior to pemetrexed plus platinum chemotherapy and most other treatment options for treatment-naïve patients with *RET* fusion-positive advanced or metastatic NSCLC. As discussed further in response to Key Issue 13 below, the submitted Company approach was heavily guided by external validation from clinicians on the long-term outcomes of patients with *RET* fusion-positive NSCLC, and the alternative parametric curves applied in scenario analyses by the EAG align less strongly with this expert opinion. Lilly request that these points are considered alongside the maturity of LIBRETTO-001 trial data.
Key issue 13: The company's choice of survival curves for the modelling of treatment effectiveness was not transparent	Yes	Lilly wish to address the key concerns raised by the EAG on Pages 135 and 136 of the EAG report. Note that Part C, related to waning of the selpercatinib treatment effect, is addressed in response to Key Issue 14, and Parts D and F, related to the estimation of PFS for pemetrexed plus platinum chemotherapy, are addressed in response to Key Issue 15. **Part A: Data immaturity of the LIBRETTO-001 trial** The immaturity of the LIBRETTO-001 trial data is discussed further in response to Key Issue 12 above.

		However, with respect to the EAG scenario analyses in which alternative PFS and OS curves were explored, Lilly acknowledge that there is uncertainty surrounding the net monetary benefit (NMB) of the intervention in these analyses. However, Lilly contest the external validity of the stratified Gompertz curve used by the EAG for the lowest OS estimates across comparators, which produces landmark survival values that are not consistent with clinical expert opinion; feedback received from expert oncologists practicing in the UK stated that OS for patients receiving selpercatinib would be around 1–10% at 20 years while the stratified Gompertz produces unreasonable estimates dropping to 0% at 10 years.[4] However, Lilly acknowledge the concerns of the EAG that the Company base case may be optimistic, and therefore an updated scenario analysis has been included in the revised economic model, which is more conservative but still within the sphere of reasonability as compared to clinical expert opinion. In this scenario analysis, the Gamma distribution is applied to the selpercatinib treatment arm, which estimates approximately 0.63% of patients remain alive at 20 years, a value beneath the lower end of the range provided by clinical experts at this timepoint (1–10%). The results of this scenario analysis are presented in Appendix G; Table 25 (Key Issue 12) and indicate that OS curve selection is not a considerable model driver, with no change in the cost-effectiveness results observed. **Part B: Curve selection** Lilly wish to reiterate that survival curve choice in the Company Submission was based principally on external validation, particularly of the associated median PFS or OS estimates. a. **Selecting the spline knot 1 distribution for OS.** As outlined in response to Clarification Question B.5, the spline knot 1 distribution was selected as the base case survival curve for OS based on its high external validity. The median OS value associated with the spline knot 1 was remarkably consistent to that observed in a real-world evidence study (Tan *et al.* 2020) evaluating OS in *RET* fusion-positive patients with NSCLC treated with a selective *RET* tyrosine kinase inhibitor ([redacted] versus 49.3 months, respectively).[25] Compared with the median OS estimates provided by clinical experts, the value utilised in the Company Submission represents a conservative estimate; both experts consulted estimated median OS to be ≥50 months in patients treated with selpercatinib. The same approach was applied to PFS, as detailed further in response to Part C of this question below. As such, whilst the use of standard parametric curves to estimate OS may have been appropriate, and might also have produced clinically plausible estimates, the spline knot 1 distribution produced the most

		externally valid landmark and median values for PFS and thus its selection is considered appropriate. b. **Additional diagnostic plots.** For completeness, plots for standard normal quantiles versus log time and log survival odds versus log time have been provided in Appendix F. Normal quantile plots can be used as a graphical tool to assess whether the fitting of a log normal distribution to a dataset is suitable. If the normal quantile plot has a linear trend, then the fitting of a log normal distribution to a particular dataset may be considered appropriate. Conversely, log survival odds plots can be used as a graphical test to assess whether the fitting of a log-logistic distribution to a dataset is suitable, with a linear trend in a log survival odds plot indicating that the fitting of a log-logistic distribution to a particular dataset may be suitable.[26] As the log survival odds plots provided in Appendix F (Figure 15–Figure 17) show a minor departure from the linear trend, it is suggested that a log-logistic distribution may not suitable to model either PFS or OS for selpercatinib nor the relevant comparators (pembrolizumab combination therapy or pemetrexed plus platinum chemotherapy) in the economic model. Whilst the normal quantile versus log time plots provided in Appendix F (Figure 10–Figure 13) show an approximately linear trend and thus may support the fitting of a log normal distribution, Lilly would like to highlight that these plots only provide information on the suitability of a survival distribution to the observed PFS and OS data. As noted in response to Part A of Clarification Question B.5, when the most appropriate function to model both PFS and OS were being selected, the external validity of the extrapolated data generated by a particular curve choice was weighted more heavily than the internal validity of a particular distribution to the observed data given the immaturity of the OS and PFS data obtained from the LIBRETTO-001 trial. Furthermore, whilst the lognormal distribution aligned with some of the long-term estimates provided by clinical experts (see Table 41 and Table 44 of Section B.3.2 of the Company submission for PFS and OS, respectively), the long tail was considered to lack external validity. For example, as outlined in response to Part I of Clarification Question B.4, the use of a lognormal curve for PFS led to [redacted]% of patients modelled to remain progression-free at 10 years, and [redacted]% progression-free at 20 years, which was considered optimistic. As such, neither a log-logistic or log-normal distribution were considered appropriate to model either PFS nor OS for selpercatinib or comparator therapies for either the company base case or scenario

		analyses. Further justification on the selection of the base case survival distributions is provided in response to other parts of this Key Issue (Parts A and C for OS and PFS, respectively). c. **Selecting the Gompertz distribution to model PFS.** As outlined in response to Part E of Clarification Question B.4, the Gompertz distribution was selected as the base case survival curve for PFS owing to its high external validity *and* clinical plausibility. As such, whilst the EAG are correct in stating that the Gompertz distribution was selected owing to its high external validity, this validity was not restricted to alignment with landmark estimates provided by clinical experts. Lilly acknowledge that in some cases, alternative distributions resulted in improved alignment with expert values than the Gompertz distribution. However, as noted in Section B.3.2.2 of the Company submission, the Gompertz distribution resulted in median PFS estimates for selpercatinib which aligned well with conservative benchmark estimates from trials in other targeted therapies (24.02 and 34.8 from the ALTA-1L and ALEX trials respectively, compared to [redacted] for the modelled arm).[27, 28] The Gompertz distribution also provided high external validity to real-world estimates for the pemetrexed plus platinum-based chemotherapy and pembrolizumab combination arms, with the modelled median PFS for each generally aligning to the results of the KEYNOTE-189 trial (4.9 and 9.0 months, respectively compared to [redacted] and [redacted], respectively, for the modelled arms).[29] In addition to alignment with both real-world values and those provided by clinical experts, the Gompertz distribution is associated with a short tail. Feedback received from clinical experts obtained in the pre-treated submission for selpercatinib (TA760) was that targeted therapies are not anticipated to be associated with a long tail.[3] Further to this, the Gompertz distribution was found to result in PFS lying below TTD for the majority of the extrapolation. This aligns with expert oncologist opinion that a proportion of patients stay on treatment post-progression for a short period of time.[4] As such, the Gompertz distribution was selected owing to its high external validity, which included alignment with real-world estimates and with expert values for all treatment arms, as well as the clinical plausibility of both the tail of the curve and the relationship between the PFS and TTD curves. Owing to the above reasons, selection of the Gompertz distribution to model PFS is considered appropriate. Lastly, Lilly wish to highlight that selection of the Gompertz distribution was conservative, as

		demonstrated by the scenario analyses conducted by the EAG (see page 135 of the EAG report) where the Gompertz distribution was associated with the lowest net monetary benefit (NMB) of all of the curves explored. As such, selection of the Gompertz distribution is likely to have impacted the cost-effectiveness results by overestimating the ICER for selpercatinib versus relevant comparators, thereby biasing results against selpercatinib. However, to address concerns raised by the EAG in Key Issue 15, updated scenario analyses exploring alternative curve choices for PFS are presented in Appendix I; Table 25. The results of these additional scenario analyses are discussed in response to Key Issue 15 below. d. **Mismatch between modelled PFS and OS and the landmark estimates informing the base case assumptions.** Lilly thank the EAG for highlighting the minor discrepancies between some of the modelled PFS and OS landmark values reported in the Table 41 and Table 44 of the Company Submission (Section B.3.2) as compared with the values seen for PFS and OS in the economic model. Please note, since HR are applied the landmark estimates for pembrolizumab combination therapy is contingent on the curve applied to the pemetrexed plus platinum chemotherapy arm. For clarity, the modelled PFS and OS tables provided in the Company submission have been updated and are provided in Appendix G for PFS (Table 20) and OS (Table 21). Lilly would like to emphasise that the corrected landmark estimates have not changed the interpretation or justification for the Company's base case curve choices or scenario analysis selection.
Key issue 14: Waning of the selpercatinib treatment effect was not explored	No	For the reasons outlined in the response to Clarification Question B10, Lilly maintain that it would be inappropriate to apply explicit treatment waning in this setting. As LIBRETTO-001 is a single arm study, no data on the head-to-head relative efficacy of selpercatinib versus a suitable comparator have been generated, meaning there is a lack of clinical data to suggest that selpercatinib efficacy relative to active comparators would decrease over time. As such, inclusion of explicit treatment effect waning is not supported by the available clinical evidence. This is further supported by consideration of hazard plots over time for selpercatinib versus comparators, as presented in Appendix E; Figure 6–Figure 9. Hazard ratios (HR) present the ratio between the hazard rate of a particular event (disease progression or death for PFS and OS, respectively) occurring in patients receiving a comparator therapy (pemetrexed plus platinum

		chemotherapy or pembrolizumab combination therapy) and the hazard rate in patients receiving selpercatinib. The hazard ratio over time for PFS and OS for selpercatinib versus both pemetrexed plus platinum chemotherapy and pembrolizumab combination was found to be greater than 1 in all instances (Appendix E; Figure 6–Figure 9), demonstrating that treatment with selpercatinib was associated with a reduced risk of both disease progression and death compared to treatment with pembrolizumab combination therapy or pemetrexed plus platinum chemotherapy over time. This remains true for the HR plots for OS for selpercatinib compared to pemetrexed plus platinum chemotherapy, which show a decreasing trend in HRs from 6 months but retain an HR consistently above 1. To provide further context to the currently presented data, Lilly would also like to highlight that that the OS data obtained from the LIBRETTO-001 trial are immature at present (median OS not reached at the latest data cut-off), meaning that robust conclusions cannot be drawn from these HR plots as the trend in HR could be subject to change over time. A clear example of the HR for selpercatinib versus a relevant comparator changing over time is provided in Figure 7 in Appendix E; the HR for PFS for selpercatinib versus pembrolizumab combination therapy temporarily decreases between 6–18 months, but then increases at a greater rate between 18 and 33 months. Furthermore, while Lilly acknowledge that there is some uncertainty surrounding these long-term outcomes, it would not be appropriate to explicitly model treatment effect waning with selpercatinib even if it is assumed to exist. This is because the survival curves implemented have been selected due to the external validity of their long-term outcomes, as validated by UK clinical experts. As such, if any treatment waning effect were to be observed with selpercatinib, it is anticipated that this has been implicitly captured in the survival curves presented in the Company Submission, and an attempt to correct for this without concrete clinical evidence could result in functional double-counting. Relatedly, alternative waning assumptions have been implicitly explored in the scenario analyses of different curve choices presented in Section B.3.10.3 (Table 72) of the Company Submission. The use of alternative curves for both PFS and OS resulted in a maximum change from the base case ICER of ±2.8% for selpercatinib versus pemetrexed plus platinum chemotherapy. Additionally, the use of alternative curve choices for OS resulted in a maximum change of ±7% of the base case ICER for selpercatinib versus pembrolizumab combination therapy. Whilst use of alternative choices for PFS resulted in the greatest change from the base case ICER for selpercatinib versus pembrolizumab combination therapy, the resultant ICERs still fell below the

		cost-effectiveness threshold, demonstrating the economic model to be robust to extrapolation curve selection for PFS and OS versus both comparators. Moreover, available evidence supports that the inclusion of efficacy waning would be clinically inappropriate. Whilst there are limited published data on the survival of patients with advanced *RET* fusion-positive NSCLC, real-world evidence from Mazieres et al. (2019) (presented in Section B.1.2.1 of Company Submission) indicates that median PFS for these patients ranged between 2.1–3.4 months, whilst median OS ranged between 10.0–21.3 months.[30] While selpercatinib is anticipated to improve patient outcomes, patients remain progression-free for a relatively short period of time given the severity of the disease. Data from the LIBRETTO-001 indicated patients treated with selpercatinib had a median PFS of 21.95 months at the latest data cut (OS data remained immature at the latest data cut).[30] This, coupled with selpercatinib being a treat-to-progression treatment (administered until patients experience a progression event), supports that the affected patient population would be unlikely to experience clinically relevant waning of selpercatinib efficacy even if it were assumed to be present.[31] Beyond the lack of clinical rationale for the application of treatment waning, it is noted that the inclusion of waning would introduce additional uncertainty to the long-term effectiveness data, given that assumptions would be needed to inform the timepoints at which waning is modelled to begin and end, and the functional form of the waning effect, and no external data are available to inform or validate these assumptions. In consideration of these clinical and methodological concerns regarding the appropriateness of including explicit treatment effect waning, additional economic analyses including explicit waning have not been presented.
Key issue 15: Potential underestimation of PFS pemetrexed plus platinum chemotherapy and hence an	No	Lilly wish to highlight that the accuracy of restricted mean survival time (RMST) approach in the determination of the observed data is inherently linked to the extent of extrapolation, and thus drawing conclusions based on RMST values is associated with complexities in the case of incomplete data. The RMST is predicated on pre-specified truncation timepoints of 1 and 1.5 years and provides an average survival time until these timepoints. Notably, the RMST is derived from Kaplan-Meier survival curves which is a non-parametric method. Conversely, the estimated lifetime horizon for this patient population that is implemented within the economic model utilises a survival prediction based on parametric distributions, and the estimation of average survival over a prolonged

overestimation of the increments versus selpercatinib		period of time means a pre-specified truncation timepoint is not necessary. Furthermore, Liao *et al*. (2020) suggest not to calculate the RMST too far away from the study follow-up to avoid too much extrapolation.[32] The key conclusion is that the average for the earlier durations of the curves would inherently have a better mean survival time than the average of the whole curve (RMST for the non-parametric KM curves versus the modelled parametric curve), which is due to the latter being 'diluted' by the tail. This does not imply the economic model has underestimated the control arm. Without any external validation via additional data sources, we can only acknowledge some potential uncertainty of the unobserved data which will always be inherent where a certain percentage of patients have not reached an event and where extrapolation of short-term data is required. Given these differences, it is not appropriate to compare the results of these two analyses directly. Furthermore, with respect to the median PFS modelled for pemetrexed plus platinum chemotherapy, Lilly do not consider the comparison made by the EAG between this value and that reported by Drilon *et al.* (2016) in a retrospective review of patients with *RET* fusion-positive adenocarcinomas (19 months) to be informative.[33] Despite being treated with pemetrexed-based therapies, the published PFS value is derived from a cohort of only 18 patients. Of these, 12 received bevacizumab-containing combination treatment, thus involving a drug with a completely distinct molecular target than those in comparator regimens included in the Company Submission.[33] As such, Lilly do not agree that it demonstrates that the modelled effectiveness of pemetrexed plus platinum chemotherapy is underestimated. In contrast, real-world evidence for the efficacy of pemetrexed plus platinum chemotherapy which indicates relative alignment with the model outcome is available: as detailed in the Company Submission, the predicted median PFS for pemetrexed plus platinum chemotherapy was [redacted] months in the submitted Company base case, while the median PFS for the same treatment in the KEYNOTE-189 trial was 4.9 months.[29] This suggests that if misalignment between the model and real-world efficacy is present, it is minimal, and possibly in the direction of an overestimation of pemetrexed plus platinum chemotherapy efficacy within the model. The minimal misalignment reflects that the matching procedure used in this case produced well-balanced data to which the model was fitted.[34] As such, while the direct efficacy of selpercatinib versus pemetrexed plus platinum chemotherapy is unknown and thus there is uncertainty regarding whether the modelled data over- or under-estimate this effect, the modelled data are well-balanced and produce results that can be considered clinically plausible based on the available evidence.

		However, to address the concerns of the EAG with respect to the potential underestimation of PFS in the model, Lilly have performed additional analyses in which the PFS analysis presented in response to Clarification Question B.23 (comparison of the observed PFS and modelled undiscounted progression free life years (LYs) at truncation timepoints of 1 year and 1.5 years) has been performed for a wider selection of PFS curve choices (Appendix H; Table 22). Following the same principle to interpret these results (observed LYs beyond observed data is >0, as described in response to Clarification Question B.23), Lilly consider that the generalised gamma, log normal, log-logistic, stratified generalised gamma, stratified log normal, stratified log-logistic and the stratified spline knot function may be interpreted as not underestimating PFS. However, for the majority of these selections, the resulting curve tail fit was implausible as compared with the long-term estimates provided by clinical experts, and several also exceeded the OS base case curves, which does not hold clinical face validity. In contrast, the generalised gamma and stratified spline knot 1 curves produced plausible PFS values for pemetrexed plus platinum chemotherapy, and thus were considered further. For each of these curves, the observed PFS by RMST and the estimated PFS across a lifetime horizon aligned most closely: the proportion of modelled data beyond the observed data was [redacted] at 1 year and [redacted] at 1.5 years for generalised gamma, and [redacted] at 1 year and [redacted] at 1.5 years for spline knot 1. Based on this alignment with observed data and with the long-term outcomes estimated by clinical experts, scenario analyses were conducted in which each of these alternative extrapolation options were selected in turn for the PFS curve. The results of these scenarios, presented in Appendix I; Table 25 indicate that PFS is not a considerable model driver, with minimal impact on the ICERs observed. This is in alignment with similar scenario analyses presented in the ingoing Company Submission (Document B, Section B.3.10.3, Table 72), where all four alternative PFS curve options had a minimal impact (±2%) on the ICER for selpercatinib versus pemetrexed plus platinum chemotherapy compared to the base case. In conclusion, while Lilly acknowledge that some uncertainty inherently exists in the estimated relative efficacy of selpercatinib versus its comparators due to a lack of head to head evidence, the base case curve choices are maintained given the use of matched data which were balanced between arms and the selection of curves which produce externally valid long-term outcomes. In addition, exploration in several scenario analyses, presented in Appendix I below and in the submitted Company Submission, demonstrate that PFS curve selection does not represent a key model driver, with the resulting ICERs robust to the use of alternative curves.

Key issue 16: Utility values were higher than the ones used in other TAs, only slightly lower than the UK general population, and had a relatively small decrement between PF and PD states	Yes	Lilly acknowledge that the utility values used in base case analysis in the Company submission were higher than those used in other technology appraisals in NSCLC and were only slightly lower than the age- and gender-matched UK general population utilities. As outlined in response to Part A of Clarification Question B.17, patients with *RET* fusion-positive NSCLC tend to be younger and fitter than the broader NSCLC population, as confirmed by clinical experts consulted as part of the NICE appraisal of selpercatinib as a second-line therapy for patients with *RET* fusion-positive advanced NSCLC (TA760).[3] These differences may mean patients are generally better able to tolerate disease progression and the associated subsequent therapies and thus may underlie the small utility decrement associated with disease progression derived from data from the SAS1 population in the LIBRETTO-001 trial. In support of this, the clinical experts consulted during TA760 considered patients with *RET* fusion-positive advanced NSCLC generally having higher utility values than people with other forms of lung cancer to be reasonable.[3] However, whilst Lilly maintain that the SAS1 population should be associated with higher utilities than the NSCLC population more broadly, it is acknowledged that the progressed disease (PD) utility value used in the original base case analysis is associated with uncertainty due to the limited number of post-progression events observed to inform it. As such, this value may be higher than what would be expected in typical clinical practice. Therefore, a revised base case approach has been provided in which the utility value for PD has been updated to the PD utility implemented in TA654, in alignment with the preferred approach of the EAG. The base case results of the updated economic model are provided in Table 11. In line with the scenario analysis presented in the original Company submission (Section B.3.10.3) in which the utility values from TA654 were implemented, these scenario analysis results showed use of the PD utility value from TA654 had a limited impact on the ICERs versus both pembrolizumab combination therapy and pemetrexed plus platinum chemotherapy.
Key issue 17: The plausibility of the company's choices for the modelling of subsequent treatments	Yes	As discussed in response to Key Issue 3 above, Lilly acknowledge that the subsequent treatment distribution presented in the original base case may not exactly match current clinical practice in the UK. Due to the limited patient number available to inform the subsequent treatments provided to patients in the LIBRETTO-001 trial, the updated base case considers the subsequent therapy distribution informed by expert clinicians, in line with the preference of the EAG. However, for completeness, scenario analyses have been performed in which subsequent treatment distributions are aligned with those reported for the SAS1 population of the LIBRETTO-

001 trial; one scenario where all subsequent treatments are included regardless of whether they are reimbursed in the NHS, and another where treatments not reimbursed by the NHS are omitted. The details of the subsequent treatment distribution implemented in each of these scenarios are presented in Table 8 and Table 9, respectively.

Lilly acknowledge the difficulty in interpreting the original tables presented in response to Clarification Question A.20 (Table 8). The way the data have been recorded by investigators makes it difficult to determine whether a patient received more than one type of therapy following progression or received some of the therapies as combinations. Therefore, the presentation of subsequent treatments from LIBRETTO-001 has been simplified below to aid interpretation and also inform the scenario analyses. In these scenarios, healthcare resource use and costs have been updated in alignment, and distribution of treatments following chemotherapy/immunotherapy and chemotherapy alone is aligned to the EAG and updated Company base case. The results of these scenario analyses are presented in Appendix G; Table 25 and demonstrate that the economic model is robust to variations in the input source for subsequent therapy distributions.

Table 8: Distribution of subsequent treatments as observed in LIBRETTO-001, including all treatments and applied in scenario analysis 17a

Therapy	% Patients after selpercatinib	% Patients after chemotherapy/ immunotherapy combination therapy	% Patients after chemotherapy
Docetaxel	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]
Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]
Pemetrexed + carboplatin	[redacted]	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]	[redacted]
Bevacizumab[a]	[redacted]	[redacted]	[redacted]
Pembrolizumab +	[redacted]	[redacted]	[redacted]

pemetrexed + carboplatin		
Paclitaxel		
Cabozantinib		
BSC		

Footnote: [a]Includes combination regimens including bevacizumab.
Abbreviations: BSC: best supportive care.

Table 9: Distribution of subsequent treatments as observed in LIBRETTO-001, omitting non-reimbursed treatments and applied in scenario analysis 17b

Therapy	% Patients after selpercatinib	% Patients after chemotherapy/ immunotherapy combination therapy	% Patients after chemotherapy
Docetaxel			
Nivolumab			
Pembrolizumab			
Atezolizumab			
Carboplatin			
Docetaxel + nintedanib			
Pemetrexed + carboplatin			
Pemetrexed			
Bevacizumab			
Pembrolizumab + pemetrexed + carboplatin			
Paclitaxel			
Cabozantinib			
BSC			

Abbreviations: BSC: best supportive care.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 10. Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
N/A	N/A	N/A	N/A

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 11. Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Ingoing Company base case ICER	***Incremental QALYs:*** • *Pemetrexed plus platinum chemotherapy: incremental QALY =* [redacted] • *Pembrolizumab combination therapy: incremental QALY =* [redacted]	***Incremental costs:*** • *Pemetrexed plus platinum chemotherapy: incremental costs =* [redacted] • *Pembrolizumab combination therapy: incremental costs =* [redacted]	***Original company base case ICERs (deterministic):*** • *Pemetrexed plus platinum chemotherapy: ICER (£/QALY) = £35,883* • *Pembrolizumab combination therapy: ICER (£/QALY) = £5,264*
Key issue 3: Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice.	Subsequent therapies distributions in the original Company base case were informed by prior technology appraisals	To align with the preference of the EAG, the subsequent therapies distributions have been updated to align with the distributions provided by UK clinical experts	• Pemetrexed plus platinum chemotherapy: ICER (£/QALY) = £40,455 (deterministic) • Pembrolizumab combination therapy: ICER (£/QALY) = £5,325 (deterministic)

Key issue 16: Health-related quality of life	The utility value for PD in the original Company base case was informed by utility data collected from LIBRETTO-001	To align with the preference of the EAG, the utility value for the PD health state has been to align with the value used in TA654.	• Pemetrexed plus platinum chemotherapy: ICER (£/QALY) = £37,396 (deterministic) • Pembrolizumab combination therapy: ICER (£/QALY) = £5,489 (deterministic)
NA	XX PAS	XX PAS	• Pemetrexed plus platinum chemotherapy: ICER (£/QALY) = £29,520 (deterministic) • Pembrolizumab combination therapy: ICER (£/QALY) = -£2,713 (deterministic)
Revised Company base case following technical engagement	**Incremental QALYs:** • Pemetrexed plus platinum chemotherapy: incremental QALY = [redacted] • Pembrolizumab combination therapy: incremental QALY = [redacted]	**Incremental costs:** • Pemetrexed plus platinum chemotherapy: incremental costs = [redacted] • Pembrolizumab combination therapy: incremental costs = [redacted]	**Revised company base case ICERs (*deterministic*):** • Pemetrexed plus platinum chemotherapy: ICER (£/QALY) = £35,542 • Pembrolizumab combination therapy: ICER (£/QALY) = -£2,776

Sensitivity analyses around revised base case

The following additional scenario analyses were explored in the revised Company model to reduce uncertainty relating to the key issues raised by the EAG:

- **Key issue 6:** Use of data from the SAS population (*RET* fusion-positive NSCLC [N=365]) as opposed to the SAS1 (treatment-naïve *RET* fusion-positive NSCLC, [N= 69]) population to inform safety data for selpercatinib (Table 25)
- **Key issue 10:** The incorporation of AEs occurring at a frequency ≥2% in any given trial arm, in line with EAG's preferred approach (Table 25)
- **Key Issue 12:** Applying the Gamma curve for OS (Selpercatinib arm only), Spline Knot 1 retained for comparator arms and Gompertz retained for PFS as per Company base case (Table 25)
- **Key issue 15**: The exploration of alternative curve choices for PFS for pemetrexed plus platinum chemotherapy (Table 25)
- **Key issue 17a:** Alignment of the subsequent therapies distributions with the LIBRETTO-001 trial, including non-reimbursed treatment options (Table 25)
- **Key issue 17b:** Alignment of the subsequent therapies distributions with the LIBRETTO-001 trial, omitting non-reimbursed treatment options (Table 25)

The results of these additional scenario analyses are provided in Appendix I; Table 25 and demonstrate the base case results to be robust to uncertainty in model inputs and assumptions.

Additionally, the probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) have been rerun, using the revised base case inputs and are presented in Appendix I.

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Appendix A: Characteristics of the UK target population

Table 12. Characteristics of patients with treatment-naive advanced NSCLC from Adelphi DSP real-world evidence insights and LIBRETTO-001 trial

Characteristics	NSCLC DSP Wave IV (N=74)	SAS1 (LIBRETTO-001) ([redacted])
Age, years		
Median	64.7	[redacted]
Sex, n (%)		
Male	39 (53)	[redacted]
Female	35 (47)	[redacted]
Race/Ethnicity, n (%)		
Hispanic/Latino	1 (1)	[redacted]
Not Hispanic or Latino	73 (99)	[redacted]
Missing	0 (0)	[redacted]
ECOG score at advanced diagnosis, n (%)		
0	11 (15)	[redacted]
1	52 (70)	[redacted]
2	7 (9)	[redacted]
3	1 (1)	[redacted]
4	3 (4)	[redacted]
Current disease stage, n (%)		
IV or greater	74 (100)	[redacted]
Investigator reported history of metastatic disease, n (%)		
Yes	NR	[redacted]
No	NR	[redacted]
Molecular assay type, n (%)		
NGS with tumour tissue	10 (37)	[redacted]

PCR on tumour	6 (22)	[redacted]
FISH on tumour	15 (56)	[redacted]
NGS on plasma/blood	0 (0)	[redacted]
Nanostring technology	0 (0)	[redacted]

Abbreviations: BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; NR: not reported; SD: standard deviation.
Source: Eli Lilly (data on file). Adelphi DSP real-world evidence insights.[35]

Appendix B: SAS1-specific adverse effects

Table 13: Treatment-emergent adverse effects (TEAEs) in the treatment-naïve subset of patients (SAS1) of LIBRETTO-001

Term, n (%)	Treatment-naïve patients (N=69)	NSCLC safety population (N=356)	Overall safety population (N=796)
Any TEAEs	69 (100.0)	356 (100.0)	795 (99.9)
Related to selpercatinib	67 (97.1)	341 (95.8)	756 (95.0)
Grade ≥3 TEAEs	50 (72.5)	263 (73.9)	572 (71.9)
Related to selpercatinib	25 (36.2)	143 (40.2)	307 (38.6)
TEAEs leading to treatment discontinuation	7 (10.1)	34 (9.6)	64 (8.0)
Related to selpercatinib	3 (4.3)	11 (3.1)	25 (3.1)
TESAEs	26 (37.7)	173 (48.6)	353 (44.3)
Related to selpercatinib	8 (11.6)	52 (14.6)	87 (10.9)
Fatal TEAEs	4 (5.8)	24 (6.7)	45 (5.7)
Related to selpercatinib	0	0	1 (0.1)

Treatment-emergent adverse events (TEAEs) are defined as adverse adverse events that start on or after the first administration of selpercatinib. Related events are those judged by the Investigator as related to selpercatinib. Severity grade assignment based on CTCAE (v4.03): Grade 3 (severe), Grade 4 (life-threatening/debilitating), Grade 5 (fatal).
Abbreviations: SAS1: supplemental analysis group 1; TEAE: treatment-emergent adverse event.
Source: EMA. Retsevmo CHMP extension of indication variation assessment report.[13]

Table 14: Serious treatment-emergent adverse effects (TEAEs) in the treatment-naïve subset of patients (SAS1) of LIBRETTO-001

Preferred term[a], n (%)	Treatment-naïve patients (N=69)	NSCLC safety population (N=356)
Drug hypersensitivity	1 (1.4)	10 (2.8)
ALT increased	1 (1.4)	6 (1.7)
AST increased	1 (1.4)	6 (1.7)
Hypersensitivity	1 (1.4)	4 (1.1)
Hypertension	0	3 (0.8)
Pleural effusion	1 (1.4)	4 (1.1)
Ascites	0	3 (0.8)
Dehydration	0	2 (0.6)

Preferred term[a], n (%)	Treatment-naïve patients (N=69)	NSCLC safety population (N=356)
Diarrhoea	0	2 (0.6)
Pericardial effusion	0	2 (0.6)
Chylothorax	0	2 (0.6)
Constipation	1 (1.4)	2 (0.6)
Drug-induced liver injury	0	1 (0.3)
Fatigue	0	1 (0.3)
Haemorrhage intracranial	0	1 (0.3)
Nausea	1	1 (0.3)
Thrombocytopenia	0	1 (0.3)
Cardiac failure	0	1 (0.3)
Colitis	0	1 (0.3)
Drug eruption	0	1 (0.3)
Dysphagia	0	1 (0.3)
ECG T wave inversion	1 (1.4)	1 (0.3)
Focal segmental glomerulosclerosis	0	1 (0.3)
Hypothyroidism	0	1 (0.3)
Ischaemic stroke	0	1 (0.3)
Liver function test increased	0	1 (0.3)
Mental disorder	0	1 (0.3)
Retroperitoneal haematoma	1 (1.4)	1 (0.3)

[a]Patients are counted once within each preferred term. Reported adverse event terms were coded using MedDRA (version 21.0). Adverse events are sorted in descending frequency based on the overall count in the overall safety analysis set.
Abbreviations: ALT: alanine transaminase; AST: aspartate transaminase; ECG: electrocardiogram; NSCLC: non-small cell lung cancer.
Source: EMA. Retsevmo CHMP extension of indication variation assessment report.[13]

Appendix C: Comparison of KEYNOTE-189 with other relevant trials

Table 15. Baseline characteristics

Study, primary author year	Treatment	Median follow-up	Cross-over allowed?	Publication year	Median age (years)	Female (%)	Asian (%)	ECOG/WHO PS					
								0		1		2	
								n	%	n	%	n	%
CameL, Zhou 2021	CAMRc+PEMc +PLATi	11.9	N	2021	60.0	28.5	100	48	23	157	77	-	-
	PEMc+PLATi	11.9		2021	60.0	28.5	100	36	17	171	83	-	-
CheckMate 227, Hellmann 2018	**PEMc+PLATi**	NR	N	2018	64	33.3	21.05	191	32.8	386	66.2		
	IPIc+NIVOc	NR		2018	64	33.3	21.05	204	35.0	377	64.7	-	-
CheckMate 9LA, Paz-Ares 2021	PEMi+PLATi+IPIc+NIVOc	13.2	N	2021	65	30	8	113	31	247	68	-	-
	PEMc+PLATi	13.2		2021	65	30	8	112	31	245	68	-	-
Doebele 2015	PEMc+PLATi+ RAMc	NR	N	2015	NA	42.12	3.53	-	-	-	-	3	4.3
	PEMc+PLATi	NR		2015	NA	42.12	3.53	-	-	-	-	4	5.6
ERACLE, Galetta 2015	**PEMc+PLATi**	27.0	Y	2015	61.0	26.1	NA	47	78	13	22	0	0
	BEVc+PACi+PLATi	27.0		2015	61.0	26.1	NA	46	79	12	21	0	0
	ATEZc	31.3	N	2020	64.0	29.2	16.2	-	-	-	-	-	-

Study, primary author year	Treatment	Median follow-up	Cross-over allowed?	Publication year	Median age (years)	Female (%)	Asian (%)	ECOG/WHO PS					
								0		1		2	
								n	%	n	%	n	%
IMPower 110, Herbst 2020	**PEMc+ PLATi**	31.3		2020	65.0	30.3	10.8	-	-	-	-	-	-
IMPower132, Nishio 2021	**PEMc+PLATi**	28.4	N	2021	63.5	33.6	23.5	114	40.1	170	59.9	-	-
	ATEZc+PEMc +PLATi	28.4		2021	63.5	33.6	23.5	126	43.2	166	56.8	-	-
IMPower132 - China, Lu 2021	ATEZc+PEMc +PLATi	11.7	N	2021	NA	NA	100	-	-	-	-	-	-
	PEMc+PLATi	11.7		2021	NA	NA	100	-	-	-	-	-	-
KEYNOTE-021, Langer 2016	**PEMc+PLATi**	49.4	Y	2016	62.9	61.0	8.0	29	46	34	54	-	-
	PEMc+PEMBROc+PLATi	49.4		2016	62.9	61.0	8.0	24	40	35	58	-	-
KEYNOTE-042, Lopes 2018	**PEMc+PLATi**	46.9	N	2018	63.0	31.0	NA	-	-	-	-	-	-
	PEMBROc	46.9		2018	64.0	30.0	NA	-	-	-	-	-	-
KEYNOTE-042 - China, Wu 2020	**PEMc+PLATi**	33.0	N	2020	NA	NA	100	29	21.6	105	78.4	-	-
	PEMBROc	33.0		2020	NA	NA	100	31	24.2	97	75.8	-	-
KEYNOTE-189, Gandhi 2018	**PEMc+PLATi**	**46.3**	**N**	**2018**	**64.5**	**41.0**	**NA**	**80**	**38.8**	**125**	**60.7**	**0**	**0**
	PEMc+PEMBROc+PLATi	46.3		2018	64.5	41.0	NA	186	45.4	221	53.9	1	0.2

Study, primary author year	Treatment	Median follow-up	Cross-over allowed?	Publication year	Median age (years)	Female (%)	Asian (%)	ECOG/WHO PS					
								0		1		2	
								n	%	n	%	n	%
KEYNOTE-189 - Japan, Horinouchi 2021	**PEMc+PLATi**	18.5	Y	2021	64.8	22.5	100	9	60	6	40	-	-
	PEMc+PEMBROc+PLATi	18.5		2021	64.8	22.5	100	15	60	10	40	-	-
Lee 2016	**PEMc+PLATi**	NR	N	2016	NA	NA	NA	-	-	-	-	-	-
	PEMc	NR		2016	NA	NA	NA	-	-	-	-	-	-
ORIENT-11, Yang 2020	SINTc+PEMc+PLATi	8.9	N	2020	61	23.7	100	76	28.6	190	71.4	-	-
	PEMc+PLATi	8.9		2020	61.0	23.7	100	34	26	97	74.0	-	-
PRONOUNCE, Zinner 2015	**PEMc+PLATi**	NR	N	2015	NA	NA	NA	85	46.7	96	52.7	-	-
	BEVc+PACi+PLATi	NR		2015	NA	NA	NA	84	46.9	95	53.1	0	0
RATIONALE 304, Lu 2021	TISLc+PEMc+PLATi	9.8	N	2021	60.3	26.1	100	54	24.2	169	75.8	-	-
	PEMc+PLATi	9.8		2021	60.3	26.1	100	24	21.6	87	78.4	-	-

Bolding indicates the relevant treatment arm of the principal study used in the indirect treatment comparison (ITC).
Abbreviations: ATEZ: atezolizumab; BEV: bevacizumab; CAM: camrelizumab; CARB: carboplatin; CIS: cisplatin; ECOG/WHO: Eastern Cooperative Oncology Group/World Health Organization; IPI: ipilimumab; NSCLC: non-small cell lung cancer; NIV: nivolumab; NR: not reported; PAC: paclitaxel; PBO: placebo; PEM: pemetrexed; PEMBRO: pembrolizumab; PLAT: platinum chemotherapy; RAM: ramucirumab; SINT: sintilimab; TIS: tislelizumab; Y: yes.

Table 16: Median follow-up and progression-free survival (first-line to progression studies)

Study ID	Intervention	Median follow-up	Median (months) (L95% CI - U95% CI)	HR (L95% CI - U95% CI)	p value
CameL, Zhou 2021	CAM+CARB+PEM+CAM (maintenance)+PEM(maintenance)	11.9	11.3 (9.6-15.4)	0.6 (0.45-0.79)	0.0001
	CARB+PEM+PEM(maintenance)	11.9	8.3 (6-9.7)	-	-
CheckMate 227, Hellmann 2018	NIV+IPI+NIV (maintenance)	-	-	0.83 (0.72-0.96)	-
	PEM+(CIS or CARB)+PEM (maintenance)	-	-	-	-
	NIV+IPI+PEM (maintenance)+NIV (maintenance)	-	5.1 (4.1-5.7)a	0.79 (0.69-0.91)	-
	PEM+(CIS or CARB)+PEM (maintenance)	-	5.5 (4.6-5.6)a	-	-
CheckMate 9LA, Paz-Ares 2021	NIV+IPI+(CARB or CIS)+PEM	13.2	7 (5.6-8.3)	0.74 (0.6-0.92)	-
	(CARB or CIS)+PEM+PEM (optional maintenance)	13.2	5.6 (4.5-5.8)	-	-
Doebele 2015	PEM+(CARB or CIS)+PEM(maintenance)	-	5.6 (4-5.7)	-	-
	RAM+PEM+(CARB or CIS)+PEM(maintenance)+RAM(maintenance)	-	7.2 (5.8-8.4)	0.75 (0.55-1.03)	0.1318
ERACLE, Galetta 2015	CIS+PEM+PEM(maintenance)	27	8.1 (7.5-10.8)	0.79 (0.53-1.17)	0.24
	CARB+PAC+BEV+BEV(maintenance)	27	8.3 (6.1-11.5)	-	-
IMPOWER 132, Nishio 2021	ATEZ+(CARB or CIS)+ATEZ (maintenance)+PEM (maintenance)	14.8	7.6 (6.6-8.5)	0.6 (0.49-0.72)	<0.0001
	CARB or CIS+PEM (maintenance)	14.8	5.2 (4.3-5.6)	-	-
	ATEZ+(CARB or CIS)+ATEZ (maintenance)+PEM (maintenance)	28.4	7.7 (6.7-8.5)	0.56 (0.47-0.67)	-
	CARB or CIS+PEM (maintenance)	28.4	5.2 (4.3-5.6)	-	-
IMPOWER 132 – China, Lu 2021	ATEZ+(CARB or CIS)+ATEZ (maintenance)+PEM (maintenance)	11.7	8.3	0.73 (0.5-1.08)	-
	CARB or CIS+PEM (maintenance)	11.7	5.8	-	-
KEYNOTE-021, Langer 2016	PEMBRO+PEM+CARB+PEM (maintenance)	24	24 (8.5-NR)	0.53 (0.33-0.86)	0.0049
	PEM+CARB+PEM optional (maintenance)	24	9.3 (6.2-14.9)	-	-
	PEMBRO+PEM+CARB+PEM (maintenance)	49.4	24.5 (9.7-36.3)a	0.54 (0.35-0.83)	-
	PEM+CARB+PEM optional (maintenance)	49.4	9.9 (6.2-15.2)a	-	-

Study ID	Intervention	Median follow-up	Median (months) (L95% CI - U95% CI)	HR (L95% CI - U95% CI)	p value
KEYNOTE-042 – China, Wu 2020	PEMBRO	33	6.3 (4.2-8.3)	1 (0.76-1.31)	
	CARB+PEM+PEM (optional maintenance)	33	6.7 (6-9)	-	-
KEYNOTE-189, Gandhi 2018, Wu 2020	PEM+(CARB or CIS)+PEMBRO	10.5	8.8 (7.6-9.2)	0.52 (0.43-0.64)	<0.001
	PEM+(CARB or CIS)	**10.5**	**4.9 (4.7-5.5)**	**-**	**-**
	PEM+(CARB or CIS)+PEMBRO	18.7	-	0.48 (0.4-0.58)	<0.00001
	PEM+(CARB or CIS)	**18.7**	**-**	**-**	**-**
	PEM+(CARB or CIS)+PEMBRO	23.1	9.0 (8.1-9.9)	0.48 (0.4-0.58)	-
	PEM+(CARB or CIS)	**23.1**	**4.9 (4.7-5.5)**	**-**	**-**
	PEM+(CARB or CIS)+PEMBRO	31	9 (8.1-10.4)	0.49 (0.41-0.59)	-
	PEM+(CARB or CIS)	**31**	**4.9 (4.7-5.5)**	**-**	**-**
	PEM+(CARB or CIS)+PEMBRO	46.3	9.0 (8.1-10.4)	0.5 (0.41-0.59)	-
	PEM+(CARB or CIS)	**46.3**	**4.9 (4.7-5.5)**	**-**	**-**
KEYNOTE-189 - Japan, Horinouchi 2021	PEM+(CARB or CIS)+PEMBRO	18.5	16.5 (8.8-21.1)	0.62 (0.27-1.42)	-
	PEM+(CARB or CIS)	18.5	7.1 (4.7-21.4)	-	-
Lee 2016	PEM+CARB	-	5.4	0.85 (0.65-1.11)	0.2353
	PEM	-	4.2	-	-
ORIENT-11, Yang 2020	SINT+PEM+(CIS or CARB)+SINT (maintenance)+PEM(maintenance)	8.9	8.9 (7.1-11.3)	0.482 (0.362-0.643)	<0.00001
	PBO+PEM+(CIS or CARB)+PBO (maintenance)+PEM(maintenance)	8.9	5.0 (4.8-6.2)	-	-
PRONOUNCE, Zinner 2015	PEM+CARB+PEM (maintenance)	-	4.40	1.06 (0.84-1.35)	0.61
	PAC+CARB+BEV+BEV(maintenance)	-	5.49	-	-
RATIONALE 304, Lu 2021	TIS+CARB+PEM+TIS(maintenance)+PEM(maintenance)	9.8	9.7 (7.7-11.5)	0.645 (0.462-0.902)	0.0044
	CARB+PEM+PEM(maintenance)	9.8	7.6 (5.6-8.0)	-	-

Bolding indicates the relevant treatment arm of the principal study used in the indirect treatment comparison (ITC).
Abbreviations: ATEZ: atezolizumab; BEV: bevacizumab; CAM: camrelizumab; CARB: carboplatin; CIS: cisplatin; HR: hazard ratio; IPI: ipilimumab; KM: Kaplan-Meier; NSCLC: non-small cell lung cancer; NIV: nivolumab; NR: not reported; PAC: paclitaxel; PBO: placebo; PEM: pemetrexed; PEMBRO: pembrolizumab; PLAT: platinum chemotherapy; RAM: ramucirumab; SINT: sintilimab; TIS: tislelizumab.

Table 17. Median follow-up and overall survival (first-line to progression studies)

Study ID	Intervention	Median follow-up	Median (months) (L95% CI - U95% CI)	HR (L95% CI - U95% CI)	p value	1 year %	2 year %	3 year %	4 year %	5 year %
CameL, Zhou 2021	CAM+CARB+PEM+CAM (maintenance)+PEM (maintenance)	11.9	NR (16.6-NR)	0.73 (0.53-1.02)	0.0330	74.9	-	-	-	-
	CARB+PEM+PEM (maintenance)	11.9	20.9 (14.2-NR)	-	-	67.1	-	-	-	-
CheckMate 227, Hellmann 2018	NIV+IPI+PEM (maintenance)+NIV (maintenance)	-	17.1 (15.2-19.9)	0.73 (0.64-0.84)	-	62	40	-	-	-
	PEM+(CIS or CARB)+PEM (maintenance)	-	13.9 (12.2-15.1)	-	-	54	30	-	-	-
CheckMate 9LA, Paz-Ares 2021	NIV+IPI+(CARB or CIS)+PEM	9.7	-	0·69 (0.55-0.87)	-	-	-	-	-	-
	(CARB or CIS)+PEM+PEM (optional maintenance)	9.7	-	-	-	-	-	-	-	-
	NIV+IPI+(CARB or CIS)+PEM	13.2	17 (14-NR)	0.69 (0.55-0.89)	-	-	-	-	-	-
	(CARB or CIS)+PEM+PEM (optional maintenance)	13.2	11.9 (9.9-14.1)	-	-	-	-	-	-	-
Doebele 2015	PEM+(CARB or CIS)+PEM(maintenance)	-	10.4 (8.2-15.9)	-	-	-		-	-	-
	RAM+PEM+(CARB or CIS)+PEM (maintenance)+RAM (maintenance)	-	13.9 (10-17.8)	1.03 (0.74-1.42)	-	-		-	-	-
ERACLE, Galetta 2015	CIS+PEM+PEM (maintenance)	27	14 (10.5-20.3)	0.93 (0.6-1.42)	-	-		-	-	-
	CARB+PAC+BEV+BEV (maintenance)	27	14.4 (10.9-19.1)	-	-	-		-	-	-
IMPOWER 132, Nishio 2021	ATEZ+(CARB or CIS)+ATEZ (maintenance)+PEM (maintenance)	14.8	18.1 (13.0-NE)	0.81 (0.64-1.03)	0.0797	59.6	-	-	-	-
	CARB or CIS+PEM (maintenance)	14.8	13.6 (11.4-15.5)	-	-	55.4	-	-	-	-
	ATEZ+(CARB or CIS)+ATEZ (maintenance)+PEM (maintenance)	28.4	17.5 (13.2-19.6)	0.86 (0.71-1.06)	-	59.7	39.1	-	-	-

Study ID	Intervention	Median follow-up	Median (months) (L95% CI - U95% CI)	HR (L95% CI - U95% CI)	p value	1 year %	2 year %	3 year %	4 year %	5 year %
	CARB or CIS+PEM (maintenance)	28.4	13.6 (11-15.7)	-	-	55	34	-	-	-
IMPOWER 132 – China, Lu 2021	ATEZ+(CARB or CIS)+ATEZ (maintenance)+PEM (maintenance)	11.7	NE	0.7 (0.4-1.24)	-	-	-	-	-	-
	CARB or CIS+PEM (maintenance)	11.7	NE	-	-	-	-	-	-	-
KEYNOTE-021, Langer 2016	PEMBRO+PEM+CARB+PEM (maintenance)	24	NR (24.5-NE)	0.56 (0.32-0.95)	-	-	67	-	-	-
	PEM+CARB+PEM optional (maintenance)	24	21.1 (14.9-NE)	-	-	-	48	-	-	-
	PEMBRO+PEM+CARB+PEM (maintenance)	49.4	34.5 (24-NR)	0.71 (0.45-1.12)	-	-	-	50	-	-
	PEM+CARB+PEM optional (maintenance)	49.4	21.1 (14.9-35.6)	-	-	-	-	37	-	-
KEYNOTE-042, Lopes 2018	PEMBRO	12.8	-	0.86 (0.72-1.03)	-	-	-	-	-	-
	CARB+PEM+PEM (optional maintenance)	12.8	-		-	-	-	-	-	-
	PEMBRO	12.8	16.7 (13.9-19.7)a	0.81 (0.71-0.93)	0.0018	-	39	-	-	-
	CARB+PEM+PEM (optional maintenance)	12.8	12.1 (11.3-13.3)a	-	-	-	28	-	-	-
	PEMBRO	14	16.4 (14-19.7)a	0.82 (0.71-0.93)	-	-	-	-	-	-
	CARB+PEM+PEM (optional maintenance)	14	12.1 (11.3-13.3)a	-	-	-	-	-	-	-
	PEMBRO	46.9	16.4 (14-19.6)a	0.80 (0.71-0.9)	-	-	-	25.3	-	-
	CARB+PEM+PEM (optional maintenance)	46.9	12.1 (11.3-13.3)a	-	-	-	-	16.7	-	-
KEYNOTE-042 - China, Wu 2020	PEMBRO	33	20.2 (17.4-25.3)a	0.67 (0.5-0.89)	-	68.8	43.8	-	-	-

Study ID	Intervention	Median follow-up	Median (months) (L95% CI - U95% CI)	HR (L95% CI - U95% CI)	p value	1 year %	2 year %	3 year %	4 year %	5 year %
	CARB+PEM+PEM (optional maintenance)	33	13.5 (10.1-17.9)a	-	-	53.5	28.2	-	-	-
KEYNOTE-189, Gandhi 2018	PEM+(CARB or CIS)+PEMBRO	10.5	NR	0.49 (0.38-0.64)	-	69.2	-	-	-	-
	PEM+(CARB or CIS)	**10.5**	**11.3 (8.7-15.1)**	**-**	**-**	**49.4**	**-**	**-**	**-**	**-**
	PEM+(CARB or CIS)+PEMBRO	18.7	22	0.56 (0.45-0.7)	<0.00001	-	-	-	-	-
	PEM+(CARB or CIS)	**18.7**	**10.7**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
	PEM+(CARB or CIS)+PEMBRO	23.1	22 (19.5-25.2)	0.56 (0.45-0.7)	-	70	45.5	-	-	-
	PEM+(CARB or CIS)	**23.1**	**10.7 (8.7-13.6)**	**-**	**-**	**48.1**	**29.9**	**-**	**-**	**-**
	PEM+(CARB or CIS)+PEMBRO	31	22 (19.5-24.5)	0.56 (0.46-0.69)	-	69.8	45.7	-	-	-
	PEM+(CARB or CIS)	**31**	**10.6 (8.7-13.6)**	**-**	**-**	**48**	**27.3**	**-**	**-**	**-**
	PEM+(CARB or CIS)+PEMBRO	46.3	22 (19.5-24.5)	0.6 (0.50-0.72)	-	-	-	31.3	-	-
	PEM+(CARB or CIS)	**46.3**	**10.6 (8.7-13.6)**	**-**	**-**	**-**	**-**	**17.4**	**-**	**-**
KEYNOTE-189 - Japan, Horinouchi 2021	PEM+(CARB or CIS)+PEMBRO	18.5	NR (NR-NR)	0.29 (0.07-1.15)	-	92	-	-	-	-
	PEM+(CARB or CIS)	18.5	25.9 (11.9-29)	-	-	80	-	-	-	-
Lee 2016	PEM+CARB	-	12.5	-	-	-	-	-	-	-
	PEM	-	9	-	-	-	-	-	-	-
ORIENT-11, Yang 2020	SINT+PEM+(CIS or CARB)+SINT (maintenance)+PEM(maintenance)	8.9	NR (NR-NR)	0.609 (0.400-0.926)	0.01921	-	-	-	-	-

Study ID	Intervention	Median follow-up	Median (months) (L95% CI - U95% CI)	HR (L95% CI - U95% CI)	p value	1 year %	2 year %	3 year %	4 year %	5 year %
	PBO+PEM+(CIS or CARB)+PBO (maintenance)+PEM(maintenance)	8.9	NR (11.4-NR)	-	-	-	-	-	-	-
PRONOUNCE, Zinner 2015	PEM+CARB+PEM (maintenance)	-	10.5	1.07 (0.83-1.36)	-	43.7	18	-	-	-
	PAC+CARB+BEV+BEV(maintenance)	-	11.7	-	-	48.8	17.6	-	-	-
RATIONALE 304, Lu 2021	TIS+CARB+PEM+TIS(maintenance)+PEM(maintenance)	9.8	-	-	-	92.7#	-	-	-	-
	CARB+PEM+PEM(maintenance)	9.8	-	-	-	84.6#	-	-	-	-

Bolding indicates the relevant treatment arm of the principal study used in the indirect treatment comparison (ITC).
Abbreviations: ATEZ: atezolizumab; BEV: bevacizumab; CAM: camrelizumab; CARB: carboplatin; CIS: cisplatin; HR: hazard ratio; IPI: ipilimumab; KM: Kaplan-Meier; NSCLC: non-small cell lung cancer; NIV: nivolumab; NR: not reported; PAC: paclitaxel; PBO: placebo; PEM: pemetrexed; PEMBRO: pembrolizumab; PLAT: platinum chemotherapy; RAM: ramucirumab; SINT: sintilimab; TIS: tislelizumab.

Appendix D: Publications used to derive NMA inputs

Table 18: Corrected Table 3.50 of the EAG report: Relative treatment effect estimates expressed as HRs of pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy

Trial	OS HR (95% CI)	PFS HR (95% CI)	Source
KEYNOTE-189 (N=616)	0.60 (0.50, 0.72)	0.49 (0.41, 0.59)	Gray J, Rodríguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, Felip E, Speranza G, De Angelis F, Dómine M, Cheng SY. FP13. 02 Pembrolizumab +Pemetrexed-Platinum vs Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189. Journal of Thoracic Oncology. 2021 Mar 1;16(3):S224.
KEYNOTE-189 Japan (N=40)	0.29 (0.07, 1.15)	0.62 (0.27, 1.42)	Horinouchi H, Nogami N, Saka H, Nishio M, Tokito T, Takahashi T, et al. Pembrolizumab plus pemetrexed-platinum for metastatic nonsquamous non-small-cell lung cancer: KEYNOTE-189 Japan Study. Cancer science. 2021;112(8):3255-65
KEYNOTE-021 (N=123)	0.71 (0.45, 1.12)	0.54 (0.35, 0.83)	Awad MM, Gadgeel SM, Borghaei H, Patnaik A, Yang JC, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Altan M, Jalal SI. Long-term overall survival from KEYNOTE-021 cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous NSCLC. Journal of Thoracic Oncology. 2021 Jan 1;16(1):162-8.

Footnote: Figures marked in bold have been updated as compared with Table 3.50 of the EAG report.
Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression free survival.

Table 19: Publications used to derive NMA input data

Study	Primary publication as presented in Appendix D.3.1 of the Company Submission	Related publications
KEYNOTE-189	Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. New England journal of medicine. 2018 May 31;378(22):2078-92.	Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non–Small-Cell Lung Cancer. 2020;38(14):1505-17
		Gadgeel SM, Garassino MC, Esteban E, Speranza G, Felip E, Hochmair MJ, et al. KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. 2019;37(15_suppl):9013

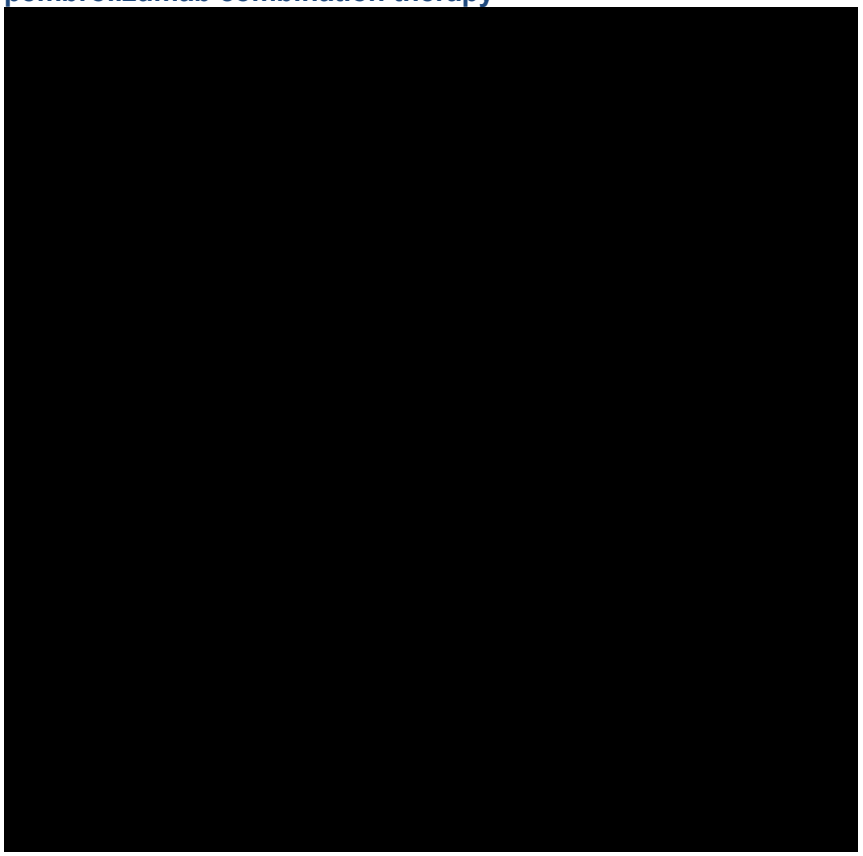
		Rodriguez Abreu D, Garassino MC, Esteban E, Speranza G, Felip E, Domine M, et al. KEYNOTE-189 study of pembrolizumab (pembro) plus pemetrexed (pem) and platinum vs placebo plus pem and platinum for untreated, metastatic, nonsquamous NSCLC: Does choice of platinum affect outcomes? Annals of Oncology. 2018;29:ix164
		Gray J, Rodríguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, Felip E, Speranza G, De Angelis F, Dómine M, Cheng SY. FP13. 02 Pembrolizumab +Pemetrexed-Platinum vs Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189. Journal of Thoracic Oncology. 2021 Mar 1;16(3):S224.
		Rodríguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, Felip E, Speranza G, De Angelis F, Dómine M, Cheng SY, Bischoff HG. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. Annals of Oncology. 2021 Jul 1;32(7):881-95.
KEYNOTE-189 Japan	**Horinouchi H, Nogami N, Saka H, Nishio M, Tokito T, Takahashi T, et al. Pembrolizumab plus pemetrexed-platinum for metastatic nonsquamous non-small-cell lung cancer: KEYNOTE-189 Japan Study. Cancer science. 2021;112(8):3255-65**	Horinouchi H, Nogami N, Saka H, Nishio M, Tokito T, Takahashi T, Kasahara K, Hattori Y, Ichihara E, Adachi N, Sawada T. Safety and tolerability of pembrolizumab or placebo plus pemetrexed and platinum as first-line therapy in Japanese patients (PTS) with metastatic non-squamous non-small cell lung cancer (NSCLC) enrolled in the phase III KEYNOTE-189 study. Annals of Oncology. 2019 Apr 1;30:ii56-7.
KEYNOTE-021	Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Jalal SI, Panwalkar A. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. The lancet oncology. 2016 Nov 1;17(11):1497-508.	Borghaei H, Langer C, Gadgeel S, Papadimitrakopoulou V, Patnaik A, Powell S, Gentzler R, Martins R, Stevenson J, Jalal S, Panwalkar A. OA 17.01 Pemetrexed-Carboplatin Plus Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC: KEYNOTE-021 Cohort G Update. Journal of Thoracic Oncology. 2017 Nov 1;12(11):S1791.
		Gentzler RD, Langer CJ, Borghaei H, Gadgeel SM, Papadimitrakopoulou V, Patnaik A, Powell SF, Martins RG, Stevenson J, Jalal SI, Panwalkar AW. 24-month overall survival from KEYNOTE-021 cohort G: Pemetrexed-carboplatin plus pembrolizumab as first-line therapy for advanced nonsquamous NSCLC.

		Borghaei H, Langer CJ, Gadgeel S, Papadimitrakopoulou VA, Patnaik A, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Jalal SI, Panwalkar A. 24-month overall survival from KEYNOTE-021 cohort G: Pemetrexed and carboplatin with or without Pembrolizumab as first-line therapy for advanced nonsquamous non–small cell lung Cancer. Journal of Thoracic Oncology. 2019 Jan 1;14(1):124-9.
		Awad MM, Gadgeel SM, Borghaei H, Patnaik A, Yang JC, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Altan M, Jalal SI. Long-term overall survival from KEYNOTE-021 cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous NSCLC. Journal of Thoracic Oncology. 2021 Jan 1;16(1):162-8.
		Awad MM, Gadgeel SM, Borghaei H, Patnaik A, Yang JC, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Altan M, Jalal SI. OFP01. 02 KEYNOTE-021 Cohort G Long-Term Follow-up: First-Line (1L) Pemetrexed and Carboplatin (PC) with or without Pembrolizumab for Advanced Nonsquamous NSCLC. Journal of Thoracic Oncology. 2021 Jan 1;16(1):S8.

Footnote: Publications marked in bold were used to inform NMA input data for the respective trials.

Appendix E: Hazard ratio plots for PFS and OS versus time

Figure 6: HR vs time of OS for selpercatinib versus pembrolizumab combination therapy

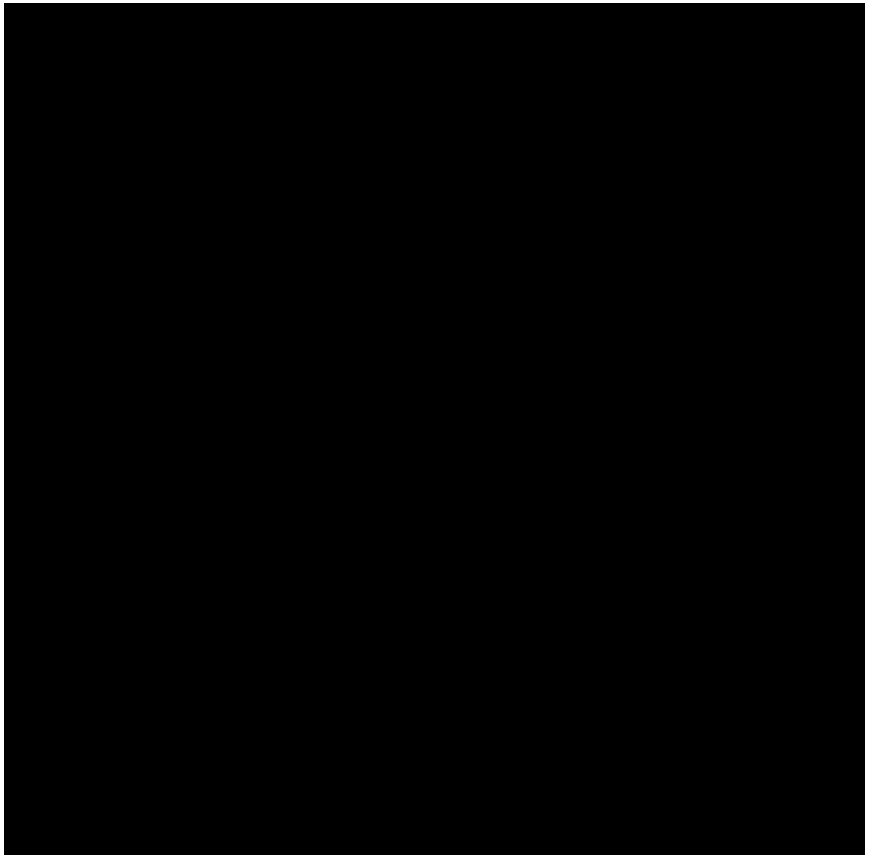


Footnote: HR = ratio of the hazard rate of death for pembrolizumab combination therapy versus hazard rate of death for selpercatinib.
Abbreviations: HR: hazard ratio; OS: overall survival.

Figure 7: HR vs time of PFS for selpercatinib versus pembrolizumab combination therapy

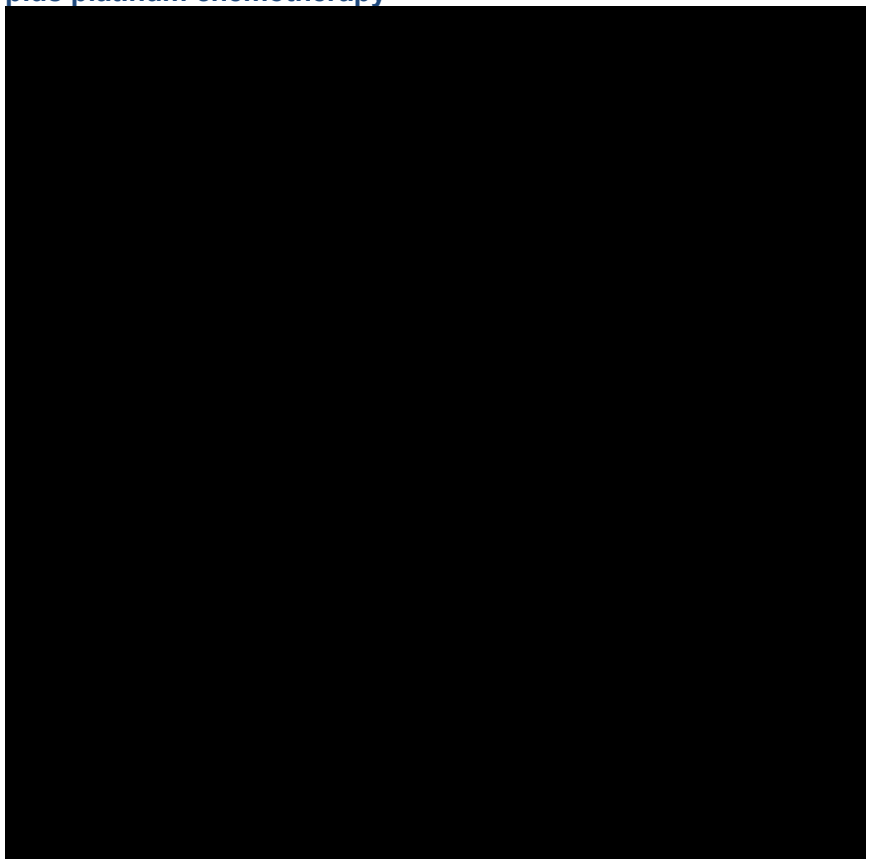
Footnote: HR = ratio of the hazard rate of progression for pembrolizumab combination therapy versus hazard rate of progression for selpercatinib.
Abbreviations: HR: hazard ratio; PFS: progression-free survival.

Figure 8: HR vs time of OS for selpercatinib versus pemetrexed plus platinum chemotherapy



Footnote: HR = ratio of the hazard rate of death for pemetrexed plus platinum chemotherapy versus hazard rate of death for selpercatinib.
Abbreviations: HR: hazard ratio; OS: overall survival.

Figure 9: HR vs time of PFS for selpercatinib versus pemetrexed plus platinum chemotherapy



Footnote: HR = ratio of the hazard rate of progression for pemetrexed plus platinum chemotherapy versus hazard rate of progression for selpercatinib.
Abbreviations: HR: hazard ratio; PFS: progression-free survival.

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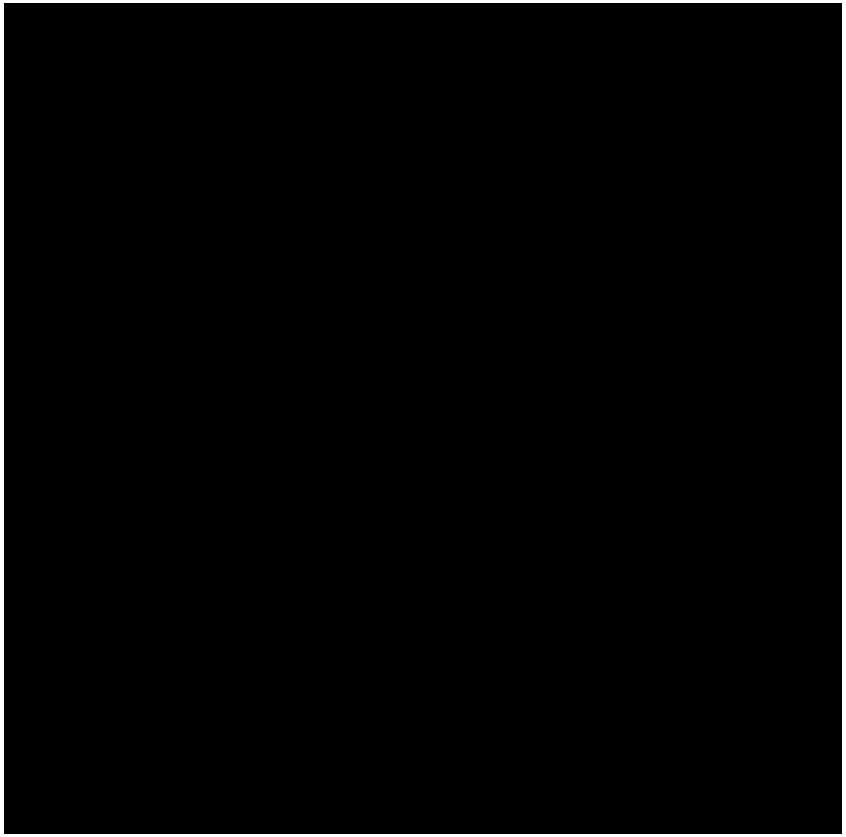
Appendix F: Diagnostic plots for parametric survival models

To address the uncertainty raised by the EAG regarding the selection of an appropriate survival curves, diagnostic plots for standard normal quantiles versus log time and log survival odds versus log time are provided below.

Figure 10: Normal quantiles vs Log(time) of OS for selpercatinib versus pembrolizumab combination therapy



Footnote: The survival probability used in the calculation of normal quantiles is from the Cox proportional hazards model.
Abbreviations: OS: overall survival.

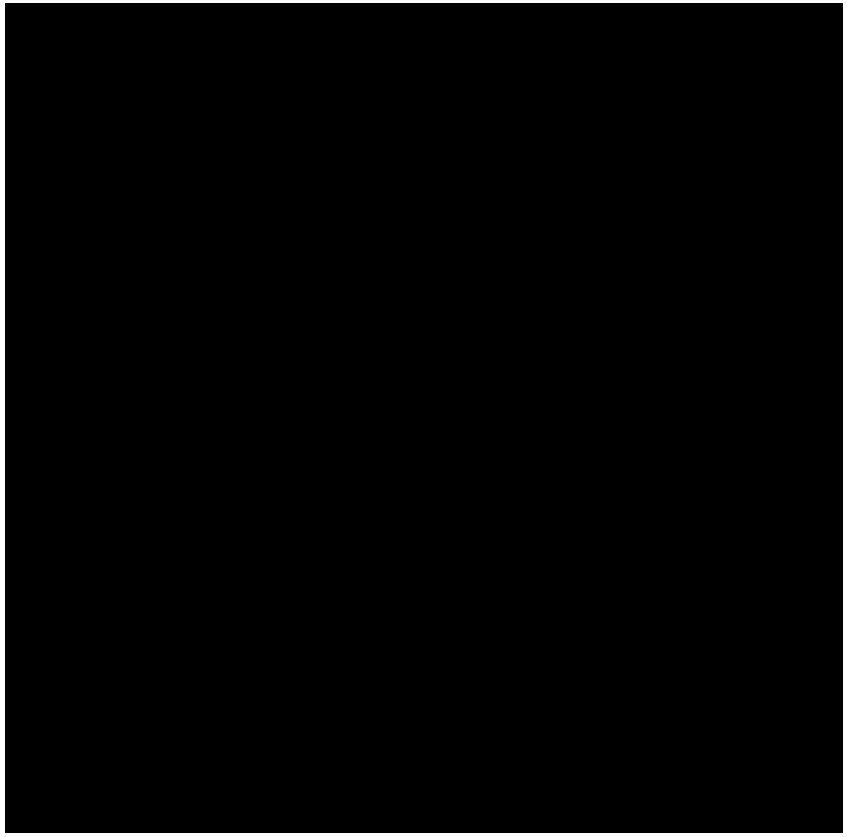
Figure 11: Normal quantiles vs Log(time) of PFS for selpercatinib versus pembrolizumab combination therapy

Footnote: The survival probability used in the calculation of normal quantiles is from the Cox proportional hazards model.
Abbreviations: PFS: progression free survival.

Figure 12: Normal quantiles vs Log(time) of OS for selpercatinib versus pemetrexed plus platinum chemotherapy

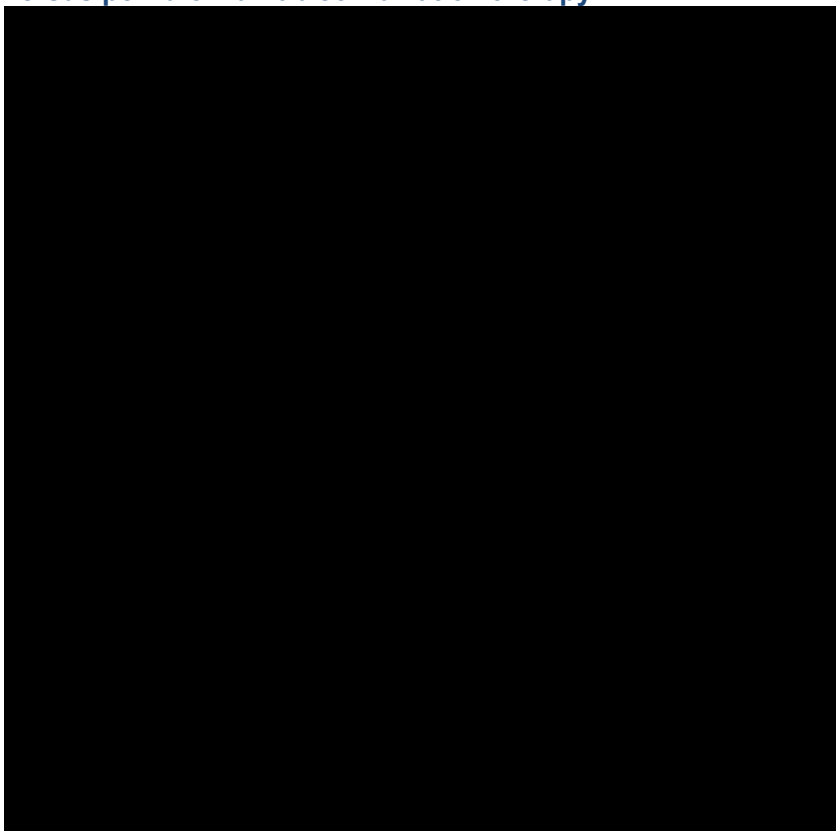
Footnote: The survival probability used in the calculation of normal quantiles is from the Cox proportional hazards model.
Abbreviations: OS: overall survival.

Figure 13: Normal quantiles vs Log(time) of PFS for selpercatinib versus pemetrexed plus platinum chemotherapy



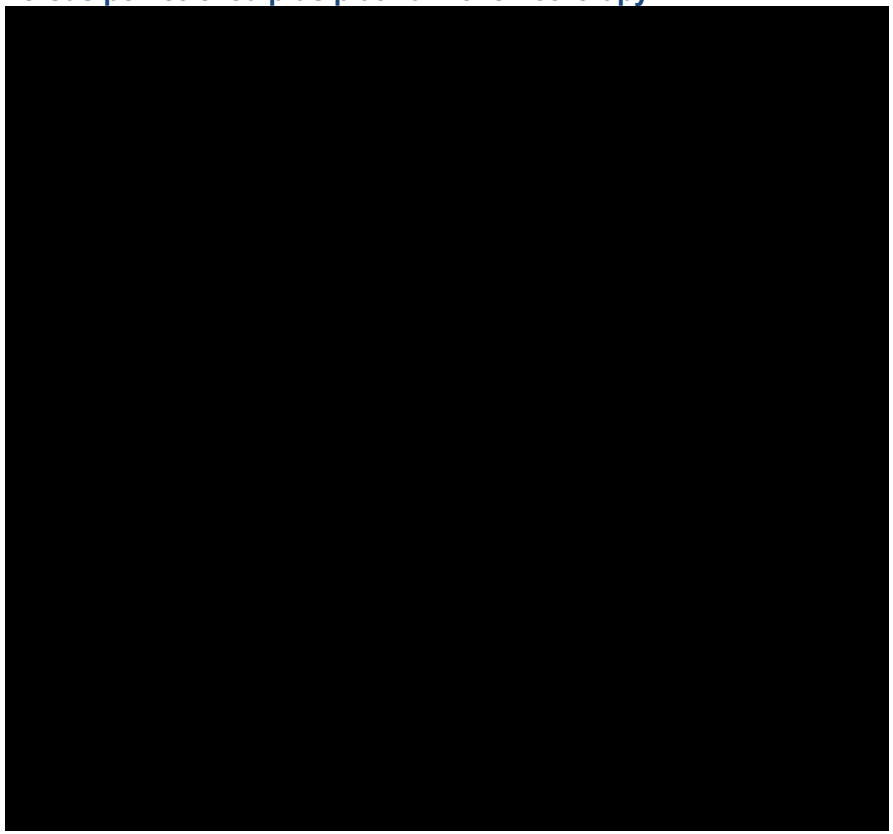
Footnote: The survival probability used in the calculation of normal quantiles is from the Cox proportional hazards model.
Abbreviations: PFS: progression free survival.

Figure 14: Log(survival odds) vs time of OS for selpercatinib versus pembrolizumab combination therapy



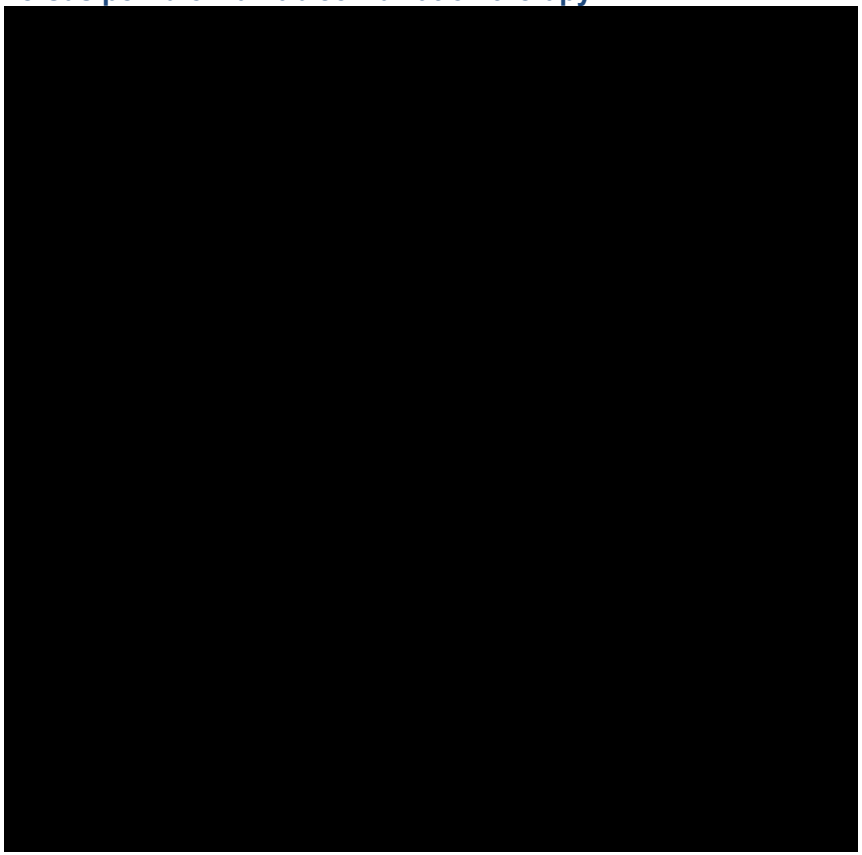
Footnote: The survival probability used in the calculation of log survival odds is from the Cox proportional hazards model.
Abbreviations: OS: overall survival

Figure 15: Log(survival odds) vs time of OS for selpercatinib versus pemetrexed plus platinum chemotherapy



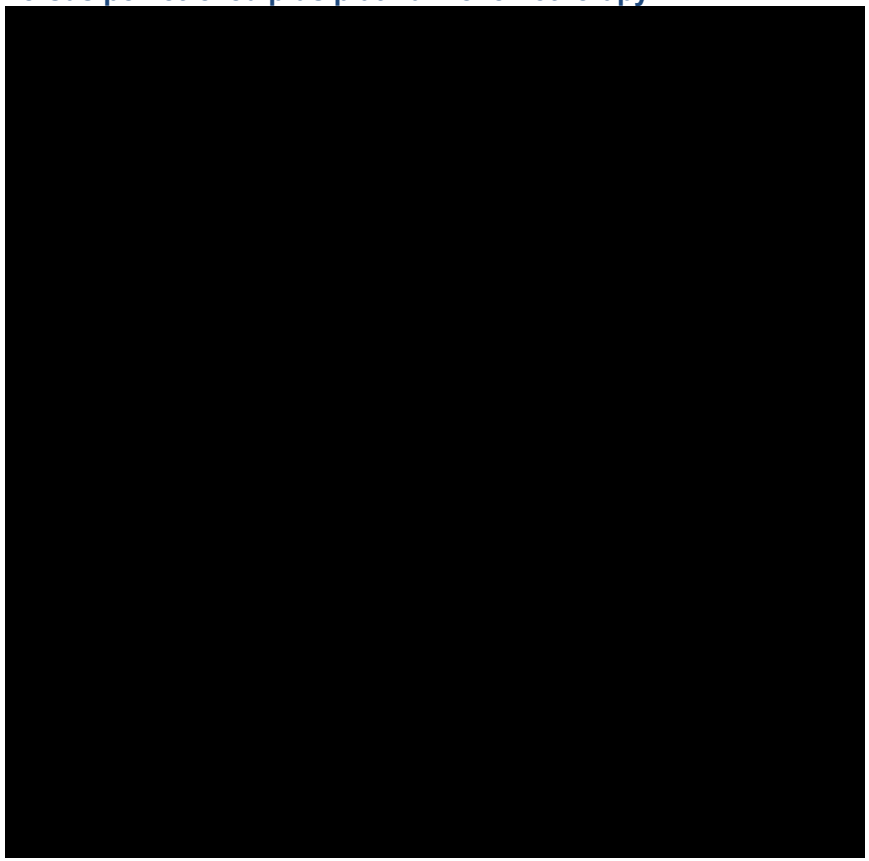
Footnote: The survival probability used in the calculation of log survival odds is from the Cox proportional hazards model.
Abbreviations: OS: overall survival

Figure 16: Log(survival odds) vs time of PFS for selpercatinib versus pembrolizumab combination therapy



Footnote: The survival probability used in the calculation of log survival odds is from the Cox proportional hazards model.
Abbreviations: PFS: progression-free survival

Figure 17: Log(survival odds) vs time of PFS for selpercatinib versus pemetrexed plus platinum chemotherapy



Footnote: The survival probability used in the calculation of log survival odds is from the Cox proportional hazards model.
Abbreviations: PFS: progression-free survival

Appendix G: Updated survival curves landmark PFS and OS estimates

Table 20: Survival curves landmark PFS estimates compared to clinical expert values

Survival curves	Selpercatinib					Pemetrexed plus platinum chemotherapy					Pembrolizumab combination therapy[a,b]				
	Median PFS (mts)	Survival (%)				Median PFS (mts)	Survival (%)				Median PFS (mts)	Survival (%)			
		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year
Exponential	[redacted]	37.08 %	19.14 %	3.66%	0.13 %	[redacted]	0.81%	0.03%	0.00%	0.00%	[redacted]	8.26%	1.57%	0.02%	0.00%
Weibull	[redacted]	33.03 %	13.29 %	1.05%	0.00 %	[redacted]	0.17%	0.00%	0.00%	0.00%	[redacted]	3.72%	0.25%	0.00%	0.00%
Generalised gamma	[redacted]	34.02 %	18.38 %	5.56%	1.02 %	[redacted]	2.80%	0.70%	0.06%	0.00%	N/A	N/A	N/A	N/A	N/A
Lognormal	[redacted]	34.35 %	19.80 %	7.30%	1.98 %	[redacted]	4.33%	1.54%	0.28%	0.04%	N/A	N/A	N/A	N/A	N/A
Loglogistic	[redacted]	33.56 %	18.78 %	7.42%	2.70 %	[redacted]	4.67%	2.19%	0.77%	0.27%	N/A	N/A	N/A	N/A	N/A
Gompertz	[redacted]	35.20 %	15.15 %	0.95%	0.00 %	[redacted]	0.51%	0.01%	0.00%	0.00%	[redacted]	6.50%	0.72%	0.00%	0.00%
Gamma	[redacted]	32.45 %	13.21 %	1.25%	0.01 %	[redacted]	0.26%	0.00%	0.00%	0.00%	N/A	N/A	N/A	N/A	N/A
Spline knot 1	[redacted]	38.57 %	21.86 %	5.68%	0.45 %	[redacted]	0.90%	0.05%	0.00%	0.00%	[redacted]	8.70%	2.03%	0.06%	0.00%
Spline knot 2	[redacted]	39.69 %	23.86 %	7.44%	0.90 %	[redacted]	1.11%	0.09%	0.00%	0.00%	[redacted]	9.72%	2.69%	0.14%	0.00%
Spline knot 3	[redacted]	42.14 %	28.96 %	13.26 %	3.71 %	[redacted]	1.39%	0.22%	0.00%	0.00%	[redacted]	10.89 %	4.16%	0.56%	0.02%

Stratified Weibull	[redacted]	33.30 %	13.66 %	1.16%	0.00 %	[redacted]	0.16%	0.00%	0.00%	0.00%	[redacted]	3.60%	0.23%	0.00%	0.00%
Stratified Generalised gamma	[redacted]	39.93 %	26.62 %	13.16 %	5.41 %	[redacted]	3.26%	1.07%	0.18%	0.02%	N/A	N/A	N/A	N/A	N/A
Stratified Lognormal	[redacted]	39.33 %	25.59 %	11.92 %	4.44 %	[redacted]	2.82%	0.82%	0.11%	0.01%	N/A	N/A	N/A	N/A	N/A
Stratified Loglogistic	[redacted]	36.55 %	22.18 %	9.89%	4.05 %	[redacted]	3.86%	1.72%	0.56%	0.18%	N/A	N/A	N/A	N/A	N/A
Stratified Gompertz	[redacted]	34.95 %	14.55 %	0.71%	0.00 %	[redacted]	0.64%	0.02%	0.00%	0.00%	[redacted]	7.32%	1.07%	0.00%	0.00%
Stratified Gamma	[redacted]	33.46 %	14.39 %	1.61%	0.02 %	[redacted]	0.22%	0.00%	0.00%	0.00%	N/A	N/A	N/A	N/A	N/A
Stratified Spline Knot 1	[redacted]	35.11 %	16.43 %	2.27%	0.04 %	[redacted]	3.84%	1.10%	0.09%	0.00%	[redacted]	18.46 %	9.63%	2.63%	0.35%
Stratified Spline Knot 2	[redacted]	36.13 %	18.21 %	3.26%	0.10 %	[redacted]	16.44 %	15.30%	13.83 %	12.43 %	[redacted]	39.22 %	37.80 %	35.86 %	33.93 %
Stratified Spline Knot 3	[redacted]	37.46 %	20.95 %	5.31%	0.40 %	[redacted]	31.18 %	40.56%	52.85 %	63.71 %	[redacted]	54.66 %	62.64 %	71.85 %	79.16 %
Expert opinion	21	30-35	15	3-5	1-5	6-11	15	<5-5	0-<1	0-<1	10-11	15	<5-5	0-<1	0-<1

Footnote: [a]Estimates were not obtained for parametric survival functions for pembrolizumab combination therapy where the proportional hazards assumption does not apply (stratified and unstratified generalised gamma, lognormal and loglogistic). [b]Estimates for pembrolizumab combination therapy is based on the base case curve (Gompertz) applied to pemetrexed+platinum chemotherapy since HR are applied for this comparison
Abbreviations:; mts: months; N/A: not applicable; NR: not reported; PFS: progression free survival.

Table 21: Survival curves landmark OS estimates compared to clinical expert values

Survival curves	Selpercatinib					Pemetrexed plus platinum chemotherapy					Pembrolizumab combination therapy[a,b]				
	Median OS (mts)	Survival (%)				Median OS (mts)	Survival (%)				Median OS (mts)	Survival (%)			
		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year		3 year	5 year	10 year	20 year
Exponential	[redacted]	61.97 %	45.05 %	20.29 %	4.12%	[redacted]	13.36 %	3.49 %	0.12 %	0.00 %	[redacted]	29.34 %	12.95 %	1.68 %	0.03 %
Weibull	[redacted]	58.67 %	36.16 %	8.69%	0.28%	[redacted]	6.38%	0.53 %	0.00 %	0.00 %	[redacted]	18.70 %	4.08%	0.05 %	0.00 %
Generalised gamma	[redacted]	59.79 %	42.53 %	21.49 %	8.05%	[redacted]	17.03 %	8.00 %	2.12 %	0.39 %	[redacted]	N/A	N/A	N/A	N/A
Lognormal	[redacted]	59.87 %	43.07 %	22.65 %	9.24%	[redacted]	18.16 %	9.11 %	2.81 %	0.65 %	[redacted]	N/A	N/A	N/A	N/A
Loglogistic	[redacted]	58.90 %	40.01 %	19.11 %	7.72%	[redacted]	15.57 %	7.90 %	2.95 %	1.07 %	[redacted]	N/A	N/A	N/A	N/A
Gompertz	[redacted]	57.55 %	26.92 %	0.08%	0.00%	[redacted]	6.12%	0.13 %	0.00 %	0.00 %	[redacted]	18.24	1.76	0.00	0.00
Gamma	[redacted]	58.50 %	36.44 %	10.00 %	0.63%	[redacted]	7.47%	0.97 %	0.00 %	0.00 %	[redacted]	N/A	N/A	N/A	N/A
Spline Knot 1	[redacted]	60.68 %	41.88 %	15.74 %	1.97%	[redacted]	9.46%	1.64 %	0.02 %	0.00 %	[redacted]	23.78 %	8.18%	0.49 %	0.00 %
Spline Knot 2	[redacted]	57.11 %	31.14 %	4.26%	0.02%	[redacted]	5.45%	0.23 %	0.00 %	0.00 %	[redacted]	16.98 %	2.49%	0.00 %	0.00 %
Spline Knot 3	[redacted]	59.22 %	37.83 %	10.54 %	0.55%	[redacted]	7.24%	0.77 %	0.00 %	0.00 %	[redacted]	20.20 %	5.14%	0.10 %	0.00 %
Stratified Weibull	[redacted]	56.63 %	30.66 %	4.11%	0.02%	[redacted]	8.00%	0.97 %	0.00 %	0.00 %	[redacted]	21.47 %	5.92%	0.16 %	0.00 %

Stratified Generalised Gamma	[redacted]	60.30 %	43.64 %	23.07 %	9.37%	[redacted]	17.12 %	8.17 %	2.27 %	0.45 %	[redacted]	N/A	N/A	N/A	N/A
Stratified Lognormal	[redacted]	60.52 %	44.21 %	24.04 %	10.30 %	[redacted]	17.58 %	8.64 %	2.57 %	0.56 %	[redacted]	N/A	N/A	N/A	N/A
Stratified Loglogistic	[redacted]	57.66 %	37.57 %	16.58 %	6.16%	[redacted]	16.47 %	8.59 %	3.33 %	1.24 %	[redacted]	N/A	N/A	N/A	N/A
Stratified Gompertz	[redacted]	56.25 %	21.65 %	0.00%	0.00%	[redacted]	11.06 %	1.80 %	0.00 %	0.00 %	[redacted]	26.15	8.65	0.20	0.00
Stratified Gamma	[redacted]	57.19 %	33.47 %	7.46%	0.29%	[redacted]	8.44%	1.27 %	0.01 %	0.00 %	[redacted]	N/A	N/A	N/A	N/A
Clinical Experts	50-72	60	45-50	20	1-10	12 to 24	25-40	6-17	<1-5	0-<1	12 to 24	25-40	6-17	<1-5	0-<1

Footnote: [a]Estimates were not obtained for parametric survival functions for pembrolizumab combination therapy where the proportional hazards assumption does not apply (stratified and unstratified generalised gamma, lognormal and loglogistic).[b]Estimates for pembrolizumab combination therapy is based on the base case curve (Spline Knot-1) applied to pemetrexed+platinum chemotherapy since HR are applied for this comparison
Abbreviations:; mts: months; N/A: not applicable; NR: not reported; PFS: progression free survival.

Appendix H: RMST analysis for pemetrexed plus platinum-based chemotherapy using alternative curve choices for PFS

Table 22: Comparison of the observed PFS, modelled undiscounted life years and modelled undiscounted progression free life years for pemetrexed plus platinum chemotherapy when using alternative curve choices

Distribution	Treatment	Observed	Modelled	
		Restricted mean survival time (RMST)	Estimated (lifetime time horizon)	Proportion beyond observed dataa
Gompertz	PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Exponential	PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Weibull	PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Gen. Gamma	PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])			
	Selpercatinib	[redacted]	[redacted]	[redacted]

	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Gamma	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Spline Knot 1	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Spline Knot 2	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Spline Knot 3	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]

lognormal	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
loglogistic	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Stratified Weibull	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Stratified Gen Gamma	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Stratified log normal	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			

	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Stratified log-logistic	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Stratified Gompertz	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Stratified Gamma	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Stratified SK-1	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Stratified SK-2	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]

	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
Stratified SK-3	**PFS - RMST period / truncation point: 1.5 years [y] (selected based on last available observation of the KN-189 trial for the control arm[b])**			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]
	PFS - RMST period / truncation point: 1 year [y] (selected based on slightly more reliable survival estimate than 1.5y)			
	Selpercatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed+platinum	[redacted]	[redacted]	[redacted]
	Increment	[redacted]	[redacted]	[redacted]

[a]Proportion beyond observed data is calculated as 100% - [Restricted mean survival time (RMST)/ Estimated (lifetime time horizon) *100]
Abbreviations: OS: overall survival; PFS: progression free survival; RMST: restricted mean survival time.

Appendix I: Updated Company base case following technical engagement

To address the key issues raised by the EAG, the following changes have been implemented to yield the Company's revised base case:

- The subsequent therapy distributions have been updated to align with the distributions provided by UK clinical experts and in line with the EAG's preference
- The utility value for the PD health state has been updated in the technical engagement model to align with the value used in TA654, in line with the EAG's preference

Revised Company base case results

The updated Company base case following technical engagement is presented in Table 23 and Table 24 for the probabilistic and deterministic analyses, respectively.

Table 23: Revised deterministic base-case results (with PAS)

Intervention	LYs	QALYs	Costs (£)	Incremental LYs	Incremental QALYs	Incremental Costs	Pairwise ICER (selpercatinib vs comparator) (£/QALY)	NHB	Fully Incremental ICER (£/QALY)
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,542	[redacted]	35,542
Pembrolizumab + pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2,776	[redacted]	Dominated
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	[redacted]	N/A

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; N/A: not applicable; NHB: net health benefit; NSCLC: non-small cell lung cancer; QALYs: quality-adjusted life years.

Table 24: Revised probabilistic base-case results (with PAS)

Intervention	LYs	QALYs	Costs (£)	Incremental LYs	Incremental QALYs	Incremental Costs	Pairwise ICER (selpercatinib vs comparator) (£/QALY)
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,542
Pembrolizumab + pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-2,646
Selpercatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; NSCLC: non-small cell lung cancer; QALYs: quality-adjusted life years.

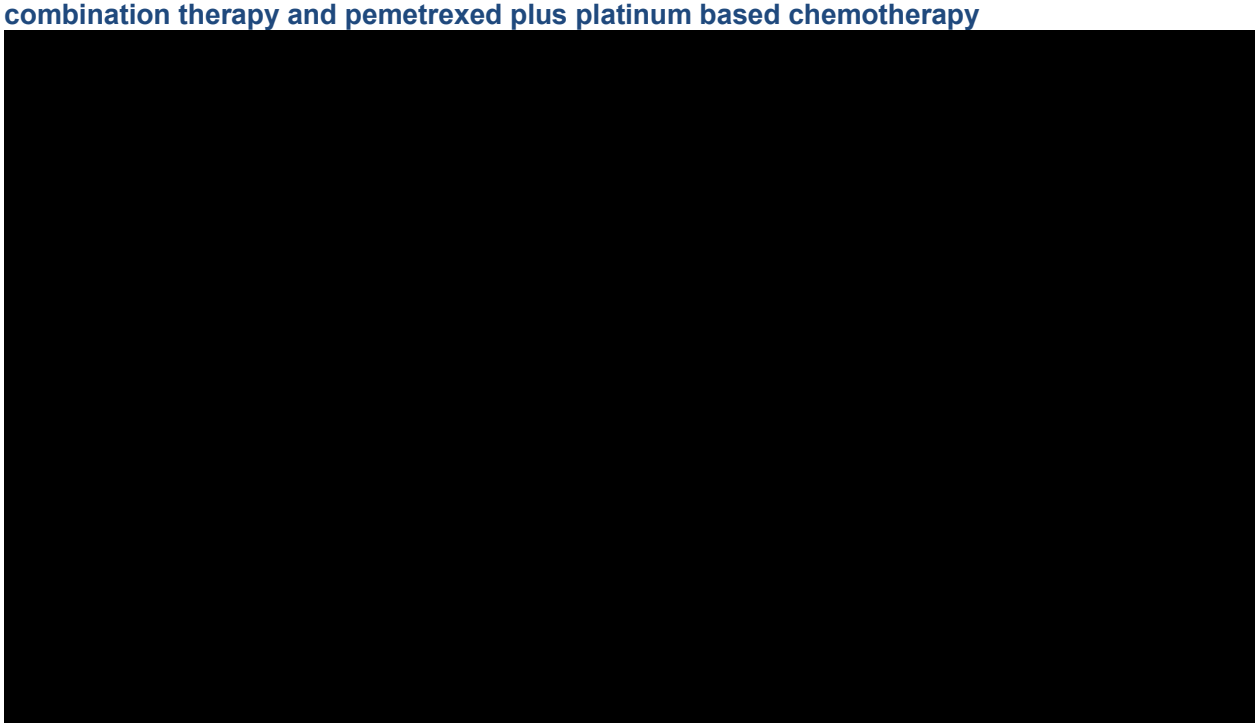
Probabilistic sensitivity analyses

The probabilistic sensitivity analyses were run in line with the methodology outlined in the Company submission on the revised Company base case inputs and are provided below.

Figure 18: Probabilistic cost-effectiveness plane for selpercatinib vs comparators

Abbreviations: QALY: quality-adjusted life year.

Figure 19: Cost-effectiveness acceptability curve for selpercatinib vs pembrolizumab combination therapy and pemetrexed plus platinum based chemotherapy



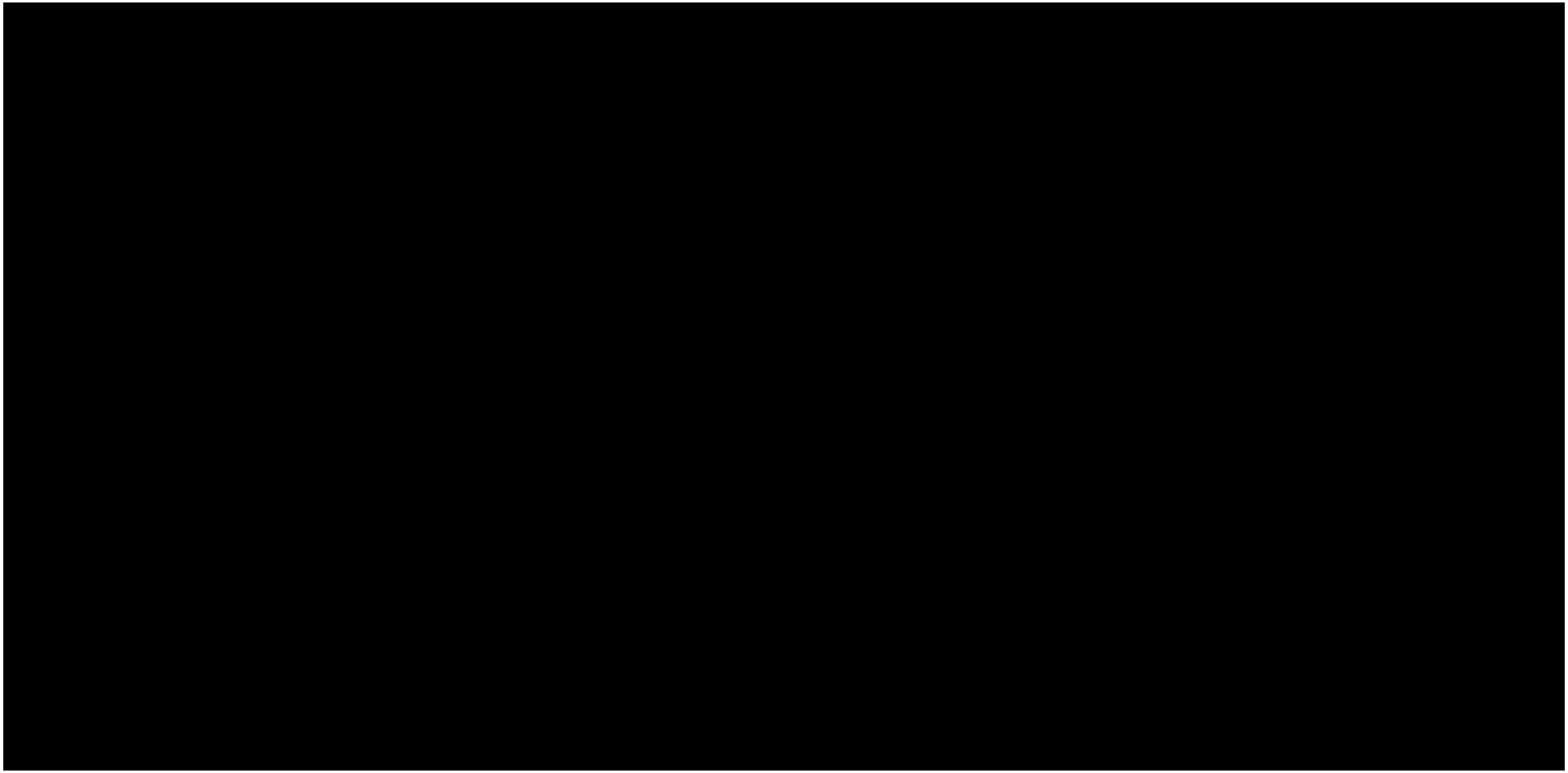
Abbreviations: QALY: quality-adjusted life year.

Deterministic sensitivity analyses

The deterministic sensitivity analyses were run in line with the methodology outlined in the Company submission on the revised Company base case inputs (Document B; Section B.3.10.2). The results are presented in Figure 20 and Figure 21.

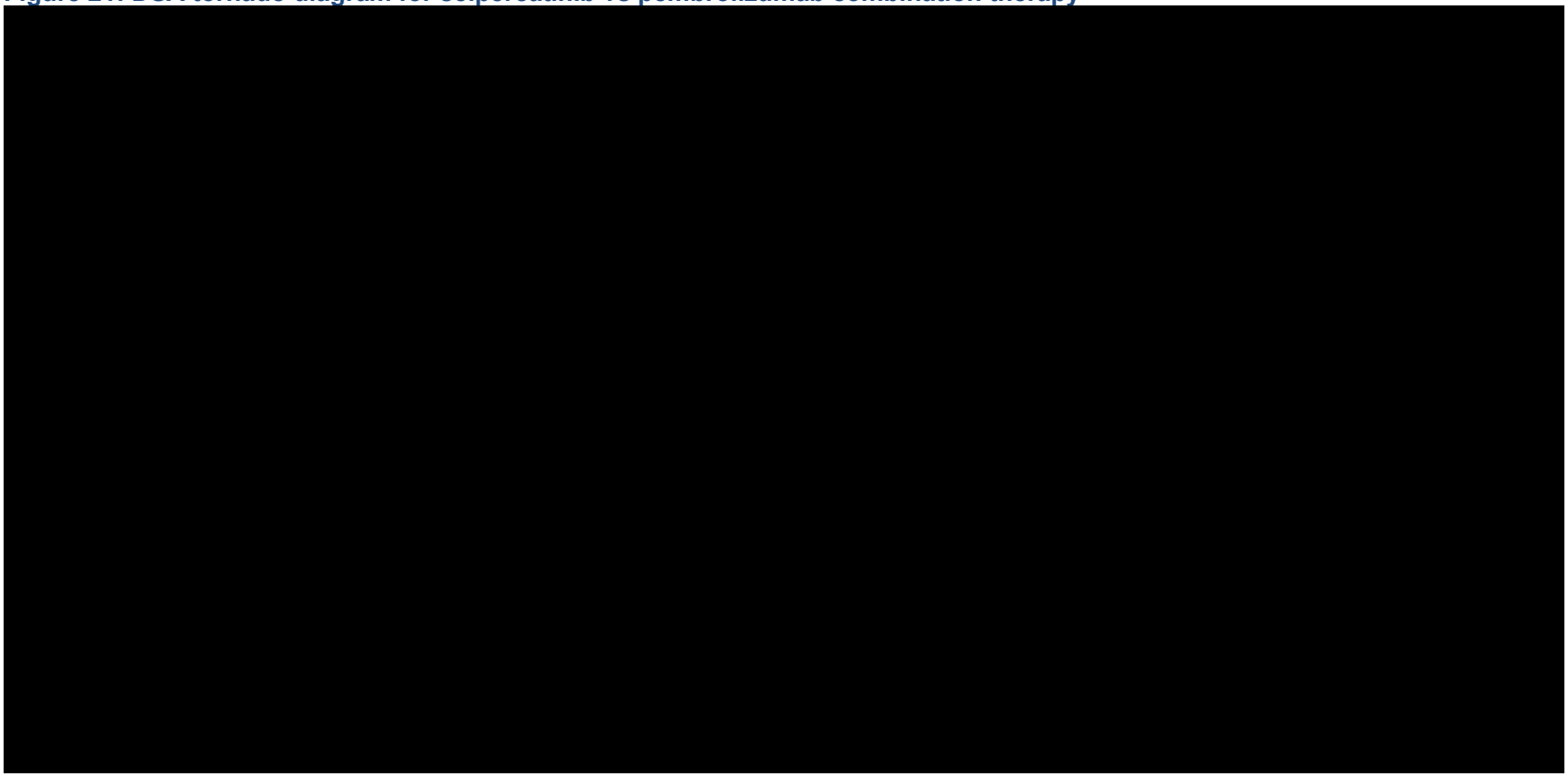
In alignment with the findings of the original Company submitted analysis only a small number of inputs had a significant impact on the ICER when varied to their limits across all pairwise comparisons and both treatment lines. For pemetrexed plus platinum-based chemotherapy, the inputs that had the greatest impact on the ICER were discount rate outcomes, discount rate costs and utility decrement for AEs. Both discount rate outcomes and discount rate costs were found to have the greatest impact on the ICER vs pemetrexed plus platinum chemotherapy in the original analysis (see Document B; Section B.3.10.2). Similarly, for pembrolizumab combination therapy, discount rate costs and outcomes were among the most influential variables, alongside drug administration costs. The three most influential variables were maintained from those found in the original analysis (discount rate costs, drug administration costs, and discount rate outcomes). Discount rate for costs and effects used in the model aligned with NICE reference case (3.5%).

Figure 20: DSA tornado diagram for selpercatinib vs pemetrexed plus platinum-based chemotherapy



Abbreviations: DSA: deterministic sensitivity analysis; ECG: electrocardiogram.

Figure 21: DSA tornado diagram for selpercatinib vs pembrolizumab combination therapy



Abbreviations: DSA: deterministic sensitivity analysis; ECG: electrocardiogram.

Scenario analyses

The results of the seven scenario analyses performed to address concerns raised by the EAG are provided in Table 25 below. Due to time constraints and owing to the high levels of consistency between the results of the deterministically and probabilistically run scenario analyses in the original Company submission (Section B.3.10.3 Table 72), all scenario analyses were run deterministically. In the majority of cases, the base case results were minimally impacted, demonstrating the economic model to be robust to uncertainty in model inputs and assumptions.

Table 25: Scenario analysis results (deterministic) for selpercatinib versus relevant comparators for the revised CEM

Scenario		Selpercatinib vs pembrolizumab + pemetrexed + platinum chemotherapy			Selpercatinib vs pemetrexed + platinum chemotherapy		
		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case[a]		[redacted]	[redacted]	***-2,776***	[redacted]	[redacted]	***35,542***
KI 6	SAS safety data	[redacted]	[redacted]	-2,003	[redacted]	[redacted]	36,177
KI10	AEs ≥2% frequency	[redacted]	[redacted]	-2,754	[redacted]	[redacted]	35,554
KI 12	OS distribution for selpercatinib: Gamma	[redacted]	[redacted]	-5,291	[redacted]	[redacted]	39,920
KI 15	PFS distribution for selpercatinib and pemetrexed plus platinum chemotherapy: Gen. gamma	-	-	-	[redacted]	[redacted]	34,188
KI 15	PFS distribution for selpercatinib and pemetrexed plus platinum chemotherapy: stratified spline-knot 1	-	-	-	[redacted]	[redacted]	34,425
KI 17a	Distribution of subsequent therapies as per LIBRETTO-001	[redacted]	[redacted]	2,898	[redacted]	[redacted]	40,048
KI 17b	Distribution of subsequent therapies as per LIBRETTO-001 (non-reimbursed treatments omitted)	[redacted]	[redacted]	-5,087	[redacted]	[redacted]	33,707

Footnote: [a]Base case results are probabilistic. All scenario analyses run deterministically.
Abbreviations: HCRU: healthcare resource use; ICER: incremental cost-effectiveness ratio; KI: Key Issue N/A: not applicable; OS: overall survival; PFS: progression-free survival; TTD: time-to-treatment discontinuation.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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 for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 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.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **17 February 2023.** 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 during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

NICE National Institute for Health and Care Excellence

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating untreated RET fusion-positive advanced 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 Shobhit Baijal
2. Name of organisation	British Thoracic Oncology Group
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with untreated RET fusion-positive advanced non-small-cell lung cancer? ☒ A specialist in the clinical evidence base for untreated RET fusion-positive advanced 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.	n/a
8. What is the main aim of treatment for untreated	To maximise survival and maintain quality of life

RET fusion-positive advanced non-small-cell lung cancer (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)	Prolongation of PFS / OS over 3 months compared with the SOC
10. In your view, is there an unmet need for patients and healthcare professionals in untreated RET fusion-positive advanced non-small-cell lung cancer?	Yes
11. How is untreated RET fusion-positive advanced 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?	Potential treatment options are: 1. Pembrolizumab plus platinum and pemetrexed 2. Platinum doublet chemotherapy (technically single agent pembrolizumab could be used if PDL1 is greater than 50% - but highly unlikely to be an effective therapy in this setting) The pathway is not well defined and there is likely significant variation across the NHS The technology would have a significant positive impact on the pathway
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? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	It would replace current care and become the first line treatment option It would be used in secondary / tertiary care centres (centres where SACT is delivered) No extra investment required. However testing pathways would need to tighten to ensure RET fusion results are available in time to make treatment decisions

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
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?	Yes Yes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	n/a
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)	It is an oral medication with potentially a safer toxicity profile. Therefore it would be easier for HCP's to use than current care
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment would start on appropriate RET fusion identification in a patient with advanced NSCLC Treatment would be stopped upon radiological and clinical disease progression
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	
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?	Yes this would be a step change in the management of the condition A targetable approach is likely to be more effective and better tolerated – reducing the potential attrition seen in lines of therapy meaning some patient with RET alterations may not receive a targeted treatment
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?	The drug has a manageable toxicity profile
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? • 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?	Yes ORR, PFS and OS
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	n/a
22. Are you aware of any new evidence for the	n/a

comparator treatment(s) since the publication of NICE technology appraisal guidance [TA683, TA181]?	
23. How do data on real-world experience compare with the trial data?	Real world is comparable
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 • 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.	n/a

Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Population: uncertainty as to whether includes squamous histology for which no evidence has been provided.	If the alteration is identified in a patient with squamous histology then access to the drug should be granted (accepting this would be a highly rare / unusual phenomenon Only a very limited number of squamous patients would be tested)
Comparators: mismatch to NICE scope and NICE guideline, which might undermine the validity of any effectiveness or cost-effectiveness estimates.	Comparator ideally should be pembrolizumab, pemetrexed and platinum

Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice.	It is difficult to match subsequent therapies that would be received in the NHS versus the subsequent treatment within Libretto-001 (being a global study – and a trial population)
Lack of comparative evidence in the correct population, which might mean treatment effect of selpercatinib overestimated and ICERs underestimated.	
Applicability: there is the possibility of differences between trial and UK target population in race and CNS metastases (due to limited information). Combined with evidence of the possibility that race and CNS metastases are effect modifiers, this implies that results from the trial may not be applicable to the UK	I disagree The trial population would match the UK target population in terms of ethnicity and brain metastases (along with other baseline characteristics)

target population.	
Adverse events: there are no specific adverse event data for the treatment naïve sub-set (SAS1 dataset) in LIBRETTO-001, or the equivalent subset of the LIBRETTO-321.	The AE management and data would expected to be the same for the treatment naïve patients as it was for the pre-treated subgroup in the study I would not expect there to be any new toxicities or for the incidence of toxicities to be different
ITC: choice of trial data (KEYNOTE-189) might have biased comparison with all comparators.	
ITC: methods of adjustment for confounding might have biased comparison with all comparators.	
NMA: heterogeneity in trials to inform pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy.	

No NMA or comparative analysis was carried out for adverse events, preventing a rigorous assessment of benefits and harms.	
Lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties in the extrapolation period.	
Immaturity of the data obtained from the LIBRETTO-001 trial for OS and PFS, adding substantial uncertainty to the extrapolated survival data in the economic model.	
The company's choice of survival curves for the modelling of treatment effectiveness was not transparent.	

Waning of the selpercatinib treatment effect was not explored.	
Potential underestimation of PFS pemetrexed plus platinum chemotherapy and hence an overestimation of the increments versus selpercatinib.	
Utility values were higher than the ones used in other TAs, only slightly lower than the UK general population, and had a relatively small decrement between PF and PD states.	
The plausibility of the company's choices for the modelling of subsequent treatments.	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Trial data in rare mutations will always be limited

From a clinical perspective the data for the treatment naïve subgroup is very positive

A targetable first line approach would be highly desirable in this situation for clinical benefit and better tolerability

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]

Technical Engagement response critique

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC+)
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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Nigel Armstrong acted as project lead and health economist/review manager on this assessment, critiqued the clinical effectiveness methods and evidence and contributing to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Bram Ramaekers, Manuela Joore, Thomas Otten, Andrea Coves Fernandez and Teebah Abu-Zarah acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mark Perry acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Robert Wolff critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Abbreviations

ACTH	Adrenocorticotropic hormone
AE(s)	Adverse event(s)
AESI	Adverse event of special interest
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATEZ	Atezolizumab
BEV	Bevacizumab
BIC	Bayesian information criteria
BICR	Blinded Independent Committee Review
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
c	Continuous
CADTH	Canadian Agency for Drugs and Technologies in Health
CAMR	Camrelizumab
CARB	Carboplatin
CASP	Critical Appraisal Skills Programme
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CEA	Carcinoembryonic antigen
CEMIPL	Cemiplimab
CENTRAL	Cochrane Central Register of Controlled Trials
Cf-DNA	Circulating free DNA
CI	Confidence interval
CIS	Cisplatin
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CR	Complete response
CrI	Credible intervals
CS	Company submission
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
Dbar	Mean sum of residual deviances
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DURV	Durvalumab
ECG	Echocardiograms
ECOG	Eastern Cooperative Oncology Group
EAG	Evidence Assessment Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
eMIT	electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ	European Platform of Cancer Research Quality of Life Questionnaire

EORTC QLQ–C30	European Platform of Cancer Research Quality of Life Questionnaire core 30
EoT	End of treatment
EQ-5D	European Quality of Life-5 Dimensions
ERL	Erlotinib
EUR	Erasmus University Rotterdam
FE	Fixing errors
FV	Fixing violations
FISH	Fluorescence in-situ hybridisation
GEF	Gefitinib
GEM	Gemcitabine
HIV	Human immunodeficiency virus
HR(s)	Hazard ratio(s)
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Appraisal
i	Induction
IA	Investigator Assessment
IAS	Integrated Analysis Set
ICER(s)	Incremental cost-effectiveness ratio(s)
ICTRP	International Clinical Trials Registry Platform
ID	Identification
iNHB	incremental net health benefit
iNMB	incremental net monetary benefit
IPD	Individual patient data
IPI	Ipilimumab
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITT	Intention to treat
JAK	Janus kinase
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Limited
LPS	Lansky Performance Score
LTFU	Lost to follow-up
LY(s)	Life year(s)
M	Maintenance
MJ	Matters of judgement
MSI	Microsatellite instability
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
N	Number of patients
n	Number of patients in specific category
N/A	Not applicable
Nab-PAC	Nab-paclitaxel
NCI CTCAE	National Cancer Institute common terminology for AEs
NCT	National Clinical Trial
NE	Not estimable
NG122	NICE guideline 122
NGS	Next generation sequencing
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIVO	Nivolumab
NL	Netherlands
NMA	Network meta-analysis

NMB	Net monetary benefit
No	Number
NR	Not reported
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
ORR	Objective response rate
ORR	Overall response rate
OS	Overall survival
OSAS	Overall Safety Analysis Set
PAC	Paclitaxel
PAS	Primary Analysis Set
PAS	Patient Access Scheme
PCB	Placebo
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death 1 receptor
PD-L1	Programmed death receptor ligand 1
PEM	Pemetrexed
PEMBRO	Pembrolizumab
PF	Progression-free
PFLY(s)	Progression-free life year(s)
PFS	Progression-free survival
PK	Pharmacokinetic
PLAT	Platinum chemotherapy
PPI	Proton pump inhibitor
PR	Partial response
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSM	Propensity score matching
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PSW	Propensity score weighting
QALY(s)	Quality-adjusted life year(s)
QD	Once daily
QLQ	Quality of life questionnaire
QoL	Quality of life
OS	Overall survival
QT	QT interval
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RP2D	Recommended Phase II dose
RAM	Ramucirumab
RANO	Response assessment in neuro-oncology criteria
RBC	Red blood cell
RCT(s)	Randomised controlled trial(s)
RDI	Relative dose intensity
RE	Random-effects
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Rearranged during transfection
RMST	restricted mean survival time
RP2D	Recommended phase 2 dose
RT	Radiation therapy

RWE	Real world evidence
SAS	Safety Analysis Set
SAS	Supplemental Analysis Set
SAS1	Supplemental Analysis Set 1
SAS2	Supplemental Analysis Set 2
SAS3	Supplemental Analysis Set 3
SCE	Summary of Clinical Efficacy
SD	Standard deviation
SD	Stable disease
SEL	Selpercatinib
SFU	Safety follow-up
SINT	Sintilimab
SIREN	Selpercatinib in RET fusion-positive non-small-cell lung cancer
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
STM	State transition model
TA(s)	Technology Appraisal(s)
TEAE(s)	Treatment emergent adverse event(s)
TISL	Tislelizumab
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
UMC+	University Medical Center+
US	United States
WHO	World Health Organization
WTP	Willingness-to-pay

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Key issue 1: Population: uncertainty as to whether includes squamous histology for which no evidence has been provided.

The company accept that no evidence is available for the efficacy and safety of selpercatinib for people with squamous RET fusion positive NSCLC, but want a recommendation to be made that Selpercatinib be provided to people with both squamous and non-squamous NSCLC.

EAG comment: The lack of evidence in the squamous RET fusion positive NSCLC population means that benefits and harms of selpercatinib in this population are unknown. Therefore, if any recommendation is extended to this population, there is a risk that they may not respond to selpercatinib, or may even experience harms. This might mean that it is not cost-effective for this group, and potentially dangerous, even after considering the cited NICE committee conclusions for a very similar STA. Effects on cost-effectiveness are unlikely to be large, as the size of the squamous sub-group is very small, but the risk of harm to individual patients with squamous pathology persists. Having said this, the EAG is also concerned that the squamous sub-group is in danger of missing a potentially beneficial treatment if selpercatinib is not made available to them if there are no biologically plausible reasons to think that the squamous population are likely to differ in their response to selpercatinib. This remains a key issue, as it is important for the committee to closely consider the benefits and harms of extending a recommendation to the squamous cell population, taking into account plausible mechanisms by which the squamous population may differ from, or concur with, the non-squamous population.

Key issue 2: Comparators: mismatch to NICE scope and NICE guideline, which might undermine the validity of any effectiveness or cost-effectiveness estimates.

The company argue that the restriction of the comparators to only 1) pembrolizumab with pemetrexed/platinum and 2) pemetrexed/platinum is justified by expert evidence and real-world evidence of a lack of efficacy and/or harm of the other NICE scope/NICE guideline comparators.

EAG comment: The EAG believes that the excluded comparators should be included in order that the effectiveness of selpercatinib versus them is estimated as robustly as possible. If some of these comparators turn out to be ineffective or harmful, after a systematic search has been carried out to ensure that all relevant studies have been properly reviewed, this will be properly reflected in the NMA results. This therefore is still a key issue.

Key issue 3: Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice.

The company acknowledges that there is a mismatch between expert opinion estimates of subsequent therapy in the UK target population and the subsequent therapy used in LIBRETTO-001. However, it believes that the data in LIBRETTO-001 are potentially non-representative, based on the sparsity of the data. In addition, the company's modelling indicates that any effects on cost effectiveness from differing subsequent therapy are likely to be small. The company also claims that the EAG preference is for clinical expert opinion instead of the LIBRETTO-001 trial.

EAG comment: The EAG agrees that estimating the distribution of subsequent therapy post-selpercatinib is challenging given no clinical practice experience. However, the EAG disputes the claim by the company of a its preference for clinical expert opinion. Indeed, despite the risk of lack of applicability to UK clinical practice, the LIBRETTO-001 trial data should be used to inform subsequent therapy distribution in the economic model as they are the only empirical source and correlated with estimates of effectiveness from the trial. Therefore, this remains a key issue.

Key issue 4: Lack of comparative evidence in the correct population, which might mean treatment effect of selpercatinib overestimated and ICERs underestimated.

The company agrees that the comparator data in the ITC differed from the selpercatinib group in terms of the RET fusion-positive status of participants. However, it defended the use of comparators with non-RET fusion-positive participants on the basis that there were no data available with RET fusion positive participants. Furthermore, it cites evidence suggesting that RET-fusion positive status does not greatly affect outcome anyway, making such differences relatively unimportant.

EAG comment: The EAG continue to contend that RET fusion positive status might affect prognosis. The data in Hess et al. 2021 suggest that RET fusion positive status actually tends to increase the hazard of death compared to non-RET fusion status [RET positive versus RET negative HR 1.52 (0.95, 2.43) for outcome of mortality], and although these effects are not significant the 95% CI only just overlaps the point of no difference with a p value close to the arbitrary threshold of 0.05(p=0.08). This might indicate that RET fusion status implies a worse prognosis and thus might favour the comparator. However, as mentioned in the EAG report, there is some evidence, albeit weak, that the median PFS of pemetrexed might be higher in the RET fusion positive population than estimated in KEYNOTE-189 (median PFS of 19 months [95% confidence interval (CI) 12–not reached (NR)] vs. no more than 9 months (see Table 4 below).[1] This therefore remains a key issue.

Key issue 5: Applicability: there is no information on the characteristics of the UK target population, meaning that comparability between trial and target population cannot be assumed

The company maintain that the SAS1 trial dataset and the UK target population are broadly comparable.

EAG comment: The EAG acknowledge the results from the UK survey (the EAG apologise for not changing the wording of this key issue on the EAG report, which implied there was no information on the characteristics of the UK target population). However, although the UK survey results showed similarities between a UK survey and the SAS1 trial dataset in age, there were differences in sex, ECOG score and molecular assay type. Although the data on ethnicity were similar between the UK survey and the SAS1 trial dataset, these data did not differentiate between important ethnic groups in the UK. No data were provided for UK patients on history of metastatic disease.

Meanwhile, the sub-group analyses demonstrated that any metastatic disease, CNS metastases, and age may be effect modifiers, and the incomplete sub-group analysis of 'race' means that 'race' cannot be excluded as an effect modifier. Whilst none of the results of the subgroup analysis were found to be statistically significant, the EAG believes that the point estimate differences are of sufficient magnitude to imply the possibility of type II errors (it is unlikely that these analyses were adequately powered, which makes type II errors more likely).

Therefore, the possibility that any metastatic disease, CNS metastases and race may differ between trial and target population (in the absence of adequate information) and the evidence that CNS metastases and race are possible effect modifiers make it possible that the effects in the trial may not be applicable to those that might be observed in the target population. This therefore remains a key issue.

Key issue 6: Adverse events: there are no specific adverse event data for the treatment naïve sub-set (SAS1 dataset) in LIBRETTO-001, or the equivalent subset of the LIBRETTO-321.

The company have provided SAS1 adverse event data in Appendix B, which have been incorporated into a scenario analysis, reported in Table 25.

EAG comment: It appears that the AE results for the NSCLC safety and SAS1 populations are very similar. The ICER increased from a company base-case of £42,175 to £42,813. Although, as described in the Updated EAG base-case section, there is some doubt as to the company base-case and it is debatable which dataset is more valid, the ICER difference is relatively small.

Key issue 7: ITC: choice of trial data (KEYNOTE-189) might have biased comparison with all comparators.

The company state that use of KEYNOTE-189 instead of any other trials evaluating pemetrexed and platinum (as the comparator in the pseudo-comparator arm) was because it was the only comparable trial with individual patient data. In addition, the KEYNOTE-189 trial was well-matched to the treatment arms of other trials included in the NMA, and so it is not thought likely that the use of the KEYNOTE-189 trial would cause bias.

EAG comment: The EAG agrees in principle that individual patient data (IPD) are useful in the context of constructing a pseudo-comparator arm, and that therefore if KEYNOTE-189 are the only relevant study with IPD then this would contribute to a justification for selecting KEYNOTE-189. However, the EAG does not think that the KEYNOTE-189 baseline data were particularly comparable to the selpercatinib data, and notes that even after propensity score matching previous smoking status was very different between arms. Therefore the EAG would have preferred the company to have presented all of the alternative pemetrexed and platinum studies (with baseline characteristics), which may have enabled a study which was more closely matched to the selpercatinib cohort (and where the need for IPD would therefore be reduced) to be used as the pseudo-comparator arm. This remains a key issue.

Key issue 8: ITC: methods of adjustment for confounding might have biased comparison with all comparators.

The company conducted an ITC using the targeted minimum loss-based estimation (TMLE) method. The results are shown Table 1.

Table 1: Estimated treatment effects for selpercatinib versus pemetrexed plus platinum chemotherapy (TMLE)

Endpoint	HR (95% CI)	p-value
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Abbreviations: Cl: confidence interval; OS: overall survival; PFS, progression-free survival; TMLE: targeted minimum loss-based estimation.

A comparison between each of the ITC methods of adjustment and the observed data of KEYNOTE-189 for median PFS and OS was also presented (see Table 2).

Table 2: Comparison of the mPFS and mOS generated via the different adjustment methods to the observed values from KEYNOTE-189 for the pemetrexed plus platinum chemotherapy arm

Adjustment method	mPFS (months)	mOS (months)
PSM	[redacted]	[redacted]
Genetic matching	[redacted]	[redacted]
PSW using generalised booster model	[redacted]	[redacted]
PSW using logistic regression	[redacted]	[redacted]

TMLE	[redacted]	[redacted]
KEYNOTE-189 (observed)[2]	4.9	10.6

Abbreviations: mPFS: median PFS; mOS: median OS; PSM: propensity score matching; PSW: propensity; TMLE: target minimum

The company concluded that the TMLE method lacked external validity because it was so different to the unadjusted estimate from KEYNOTE-189. The company also cited the other 15 clinical trials of pemetrexed plus platinum chemotherapy in the SLR, stating that median PFS was lower than 9 months in all but one, which had 'large confidence intervals' and that "…a median PFS of approximately 5–6 months was typically observed."

EAG comment: The EAG does not understand why the TMLE method was used given that no justification was provided for its choice and that it is not mentioned in TSD 17. However, the higher HRs than with the methods already conducted (see EAG report) and the longer mPFS do not seem to be implausible given that at least one of the trials cited by the company had a mPFS greater than 9.0 and the values of 5-6 described as being 'typically observed' were higher than all of the ones estimated by the other methods of adjustment. In fact, the EAG cited a study showing a PFS of 19 months, which, albeit small (n=19), was in the correct population of RET fusion positive. Therefore, although the EAG do not believe that the TMLE method is superior, it does highlight the uncertainty in methods of adjustment and supports the possibility that the treatment effect of selpercatinib vs. pemetrexed plus platinum chemotherapy might have been overestimated in the company base case. This therefore remains a key issue.

Key issue 9: NMA: heterogeneity in trials to inform pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy.

The company provided a correction to the data input into the NMAs carried out by the EAG, as presented in Section 3.5 of the EAG report.

EAG comment: The corrected version shows that there is no effect on the point estimates of the OS and PFS HRs of excluding KEYNOTE-189-Japan. This is therefore no longer a key issue.

Key issue 10: No NMA or comparative analysis was carried out for adverse events, preventing a rigorous assessment of benefits and harms

The company have argued that a comparative analysis of AEs is not feasible because there are multiple types in the economic model, each informed by few data and thus associated with too much uncertainty. They also argues that there was too much heterogeneity with SAEs being reported up to 28 days in LIBRETTO-001 vs. up to 90 days in KEYNOTE-189. Finally, they also stated that LIBRETTO-001 was not powered on the safety data.

EAG comment: All the arguments by the company are spurious. Firstly, there is no logical reason that a comparative analysis of clinical effectiveness should be determined by the data used in the cost-effectiveness analysis: indeed, it is always the case that there comparisons of more outcomes in the former than used in the latter. Secondly, the heterogeneity by follow-up time would have been reduced by the estimation of rates (per unit time) of AEs. Thirdly, the lack of a plan to power a trial to detect an outcome of a particular magnitude is not a reason for not considering that outcome for inference and decision making. In fact, the outcome that is of relevance for decision making is the treatment effect i.e., the difference between the outcomes for selpercatinib and the comparators, which the LIBRETTO-001 trial could not have been powered for given that it only had a single arm. The EAG therefore conclude that lack of comparison of adverse events remains a key issue.

Key issue 11: Lack of an STM to assist in verifying the plausibility of PSM extrapolations and to address uncertainties in the extrapolation period.

The company repeats its arguments why it maintains that the employment of a PSM is appropriate and does not intend to present an STM.

EAG comment:

No compelling new arguments or evidence provided. Hence, the EAG perspective as described in the EAG report remains unchanged.

Key issue 12: Immaturity of the data obtained from the LIBRETTO-001 trial for OS and PFS, adding substantial uncertainty to the extrapolated survival data in the economic model

The company acknowledges that the maturity of the data obtained from the LIBRETTO-001 trial should be considered in the interpretation of the economic model, but noted that the current interim analysis (15th June 2021) data were highly promising. The company expects further data-cuts will be available [redacted].

EAG comment:

No compelling new arguments or evidence provided. Hence, the EAG perspective as described in the EAG report remains unchanged.

Key issue 13: The company's choice of survival curves for the modelling of treatment effectiveness was not transparent

The company addresses the key concerns related to data immaturity of the LIBRETTO-001 trial and survival curve choice transparency raised by the EAG:

Part A: data immaturity of the LIBRETTO-001 trial

The company acknowledges that there is uncertainty surrounding the net monetary benefit (NMB) of the intervention in these analyses, but it contested the external validity of the stratified Gompertz curve used by the EAG. The company performed an updated scenario analysis applying the Gamma distribution to the selpercatinib treatment arm. The company further argues that the results of this analysis indicate that OS curve selection is not a considerable model driver, with no change in the cost-effectiveness results observed.

Part B: curve selection

The company reiterates that curve choice in the CS was based principally on external validation, particularly of the associated median PFS or OS estimates.

a. The company argues that, whilst the use of standard parametric curves to estimate OS may have been appropriate, the spline knot 1 distribution produced the most externally valid landmark and median values for PFS and thus its selection is considered appropriate.

b. The company provided plots for standard normal quantiles versus log time and log survival odds versus log time in Appendix F and provided their interpretation of these plots.

c. The company states that the Gompertz distribution was selected owing to its high external validity, which included alignment with real-world estimates and with expert values for all treatment arms, as well as the clinical plausibility of both the tail of the curve and the relationship between the

PFS and TTD curves. The company acknowledges that in some cases, alternative distributions resulted in improved alignment with expert values than the Gompertz distribution.

d. The company thanks the EAG for highlighting the minor discrepancies between some of the modelled PFS and OS landmark values reported in the Table 41 and Table 44 of the CS as compared with the values seen for PFS and OS in the economic model. The company updated the modelled PFS and OS tables provided in the CS and provided these.

EAG comment:

Part A: data-immaturity of the LIBRETTO-001 trial

To quantify the uncertainty surrounding the immaturity of the LIBRETTO-001 trial data, the EAG explored a range of plausible PFS and OS curves that may be informative to the committee. As stated in the EAG report, plausibility was based on 1) the curve being closer to an expert estimate or external data than the curve chosen by the company, and 2) the curve having a plausible shape. The EAG acknowledges that its analysis using the stratified Gompertz curve was at the pessimistic end of the explored range of curves, but it was not considered implausible. In addition, the EAG does not agree with the company that the results of their analysis applying the Gamma curve to the selpercatinib arm indicates that OS curve selection is not a considerable model driver, as this analysis substantially increased the ICER for the comparison versus pemetrexed + platinum chemotherapy.

Part B: curve selection

The EAG would like to emphasize that, regardless of which survival curves are selected, there is substantial uncertainty around the extrapolated survival data in the economic model due to the immaturity of the selpercatinib OS and PFS data from the LIBRETTO-001 (42% had progressed and 29% had died).

a. The EAG appreciates the company's further justification of selecting the spline knot 1 model for OS. Nevertheless, as stated in the NICE DSU TSD 21 guidance, more complex survival curves should be considered when hazard functions are observed, or expected in the longer-term, to have complex shapes (i.e., where there are two or more turning points, or where there are two or more important changes in the hazard function slope). Hence, the EAG would like to see further justification by the company regarding the complexity of the observed and expected OS hazard functions, guided by NICE DSU TSD 21, and how the spline knot 1 model aligns with this as opposed to standard parametric curves.

b. The EAG appreciates that the requested standard normal quantiles versus log time and log survival odds versus log time were provided by the company. Although the EAG generally agrees with the company's interpretation of these plots, based on solely a visual examination of these plots it cannot draw conclusions on the suitability of the log-normal and log-logistic curves for the modelling of PFS and OS.

c. The EAG would like to note that, as reported in CS Table 42, median PFS estimates for selpercatinib resulting from (almost all) other parametric curves were also well aligned with the benchmark estimates from the ALTA-1L and ALEX trials, as well as real-world estimates for the pemetrexed plus platinum-based chemotherapy and pembrolizumab combination arms. Nevertheless, the EAG agrees with the company that the Gompertz curve was at the conservative end of the range of curves that was explored in EAG scenario analyses, although it should be noted that in these analyses OS and PFS were varied simultaneously.

d. The EAG compared the updated OS and PFS tables in Appendix G of the technical engagement response to the values in the economic model. Although the differences are minor, there still appears to be a mismatch between the reported numbers in the tables and the values in the economic model. Therefore, this remains an issue.

Key issue 14: Waning of the selpercatinib treatment effect was not explored

The company maintains that it would be inappropriate to apply explicit treatment waning in this setting for their reasons outlined in the CS and response to clarification question B10. As requested by the EAG, the company provided hazard ratio plots versus time for OS and PFS in appendix E of the technical engagement response.

EAG comments:

Apart from the hazard ratio plots and the company's interpretation of these plots, no compelling new arguments or evidence were provided.

The company states that "The hazard ratio over time for PFS and OS for selpercatinib versus both pemetrexed plus platinum chemotherapy and pembrolizumab combination was found to be greater than 1 in all instances, demonstrating that treatment with selpercatinib was associated with a reduced risk of both disease progression and death compared to treatment with pembrolizumab combination therapy or pemetrexed plus platinum chemotherapy over time. This remains true for the HR plots for OS for selpercatinib compared to pemetrexed plus platinum chemotherapy, which show a decreasing trend in HRs from 6 months but retain an HR consistently above 1".

Although the EAG agrees that the hazard ratios over time for PFS and OS in all provided plots were greater than 1, especially the decreasing trend in the OS and PFS hazard ratio plots versus pemetrexed plus platinum chemotherapy towards a hazard ratio of 1 suggests potential waning of the selpercatinib treatment effect. Based on this and considering the uncertainty resulting from the immature LIBRETTO-001 data, the EAG's perspective as described in the EAG report remains unchanged and it would like to see an updated model and scenario analyses exploring the impact of waning of the selpercatinib treatment effect.

Key issue 15: Potential underestimation of PFS pemetrexed plus platinum chemotherapy and hence an overestimation of the increments versus selpercatinib

The company highlights potential issues of using restricted mean survival time approach to determine the observed (progression-free) survival. Moreover, the company questions the EAGs comparison of the modelled median PFS for pemetrexed plus platinum chemotherapy and a retrospective review by Drilon et al. (2016. The company performed additional analyses in which the PFS analysis presented in response to Clarification Question B.23 has been performed for a wider selection of PFS curve choices, arguing that the generalised gamma and stratified spline knot 1 curves produced the most plausible PFS values for pemetrexed plus platinum chemotherapy. The company in conclusion acknowledges that some uncertainty inherently exists in the estimated relative efficacy of selpercatinib versus its comparators due to a lack of head to head evidence, the base case curve choices are maintained given the use of matched data which were balanced between arms and the selection of curves which produce externally valid long-term outcomes.

EAG comment:

Although the EAG appreciates the provided information and additional analyses, it believes that the conclusions related to the company's base-case analyses are still valid:

"These findings indicate that the large majority of (PF)LY gains are accumulated beyond the observed data period and hence additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted (as requested but not provided in the company's response to clarification question B23). This includes verifying the plausibility of the partitioned survival model extrapolations (see Section 4.2.2). In addition to the above, it is noticeable that the observed PFS for pemetrexed + platinum chemotherapy (based on a 1.0 year or 1.5-year time horizon) is larger than the modelled PFS based on a lifetime time horizon. This might suggest that PFS for pemetrexed + platinum chemotherapy is underestimated and hence the increments versus selpercatinib potentially overestimated (see Section 4.2.6)."

Hence, in addition to the information provided, it would be informative if the company could further elaborate on the plausibility of the (PF)LY gains accumulated beyond the observed data period. Additionally, independently of the impact of using alternative PFS curves, it would be informative if the company could elaborate on the plausibility that the observed PFS for pemetrexed + platinum chemotherapy (based on a 1.0 year or 1.5-year time horizon) is larger than the modelled PFS.

Key issue 16: Utility values were higher than the ones used in other TAs, only slightly lower than the UK general population, and had a relatively small decrement between PF and PD state

The company repeats its arguments why RET fusion-positive NSCLC patients are expected to generally have higher utility values than patients with other forms of lung cancer. However, the company acknowledges that the progressed disease (PD) utility value used in the original base case analysis is associated with uncertainty due to the limited number of post-progression events observed to inform it. Therefore, a revised base case approach has been provided in which the utility value for PD has been updated to the PD utility implemented in TA654, in alignment with the preferred approach of the EAG.

EAG comment:

The EAG appreciates that the company aligned its base-case PD utility with the EAG's preferred approach. No compelling new arguments or evidence were provided with regards to the PF utility.

Key issue 17: The plausibility of the company's choices for the modelling of subsequent treatments

The company acknowledges that the subsequent treatment distribution presented in the original base case may not exactly match current clinical practice in the UK. Due to the limited patient number available to inform the subsequent treatments provided to patients in the LIBRETTO-001 trial, the updated base case considers the subsequent therapy distribution informed by expert clinicians, which is stated to be in line with the preference of the EAG. The company also performed scenario analyses in which subsequent treatment distributions are aligned with those reported for the SAS1 population of the LIBRETTO-001 trial.

EAG comment:

The EAG would like to stress that, contrary to what was stated by the company in its response to technical engagement, it does not prefer to inform subsequent treatments post selpercatinib based on expert opinion. Alternatively, as stated in the EAG report, the EAG ideally informs subsequent treatments post selpercatinib based on data from the LIBRETTO-001 trial. However, this was not possible at an earlier stage, as the information provided by the company in Table 32 of the clarification response was not transparent.

The EAG appreciates that the company provided the requested scenario analyses informing subsequent treatment distributions based on the SAS1 population of the LIBRETTO-001 trial. There are, however,

several unclarities to the EAG in the scenario analysis where treatments not reimbursed by the NHS are omitted: 1) As there is currently no experience of subsequent treatments post-selpercatinib at this line, the EAG would assume that all second-line treatments in the NICE guideline CG122 care pathway would be a subsequent treatment option for RET fusion+ patients.[3] It is therefore unclear to the EAG why pembrolizumab was omitted as a subsequent treatment option post-selpercatinib. 2) It is unclear to the EAG why post-selpercatinib subsequent therapies consist of carboplatin, pemetrexed and paclitaxel monotherapy, given that none of these are part of the second-line treatments in the NICE guideline CG122 care pathway for RET fusion+ patients.

As stated in key issue 3 above, the EAG considers that the LIBRETTO-001 trial data should be used to inform subsequent therapy distribution in the economic model as they are the only empirical source and correlated with estimates of effectiveness from the trial. Considering the inconsistencies in the company's scenario analysis where treatments not reimbursed by the NHS were omitted, despite the risk of lack of applicability to UK clinical practice, the analysis informing subsequent treatment distributions post selpercatinib based on all subsequent treatments included in LIBRETTO-001 regardless of whether they are reimbursed in the NHS is adopted by the EAG in its base-case.

Updated EAG base-case

The EAG identified a potential error in the company's updated base-case results following technical engagement. The company's changes to their base-case are reported in Table 11 of the technical engagement response and include changes to 1) the subsequent therapies distributions and 2) the utility value for the PD health state. In an attempt to verify the results from Table 11, the EAG found that the revised company base-case results following technical engagement also include the different approach of modelling AEs (≥2% difference between arms rather than between patients) as described in key issue 10. For the results below, the EAG assumes that this was not the intention of the company and deterministic ICERs of £42,187 per QALY versus pemetrexed + platinum chemotherapy (instead of £42,175 per QALY) and £5,599 per QALY versus pembrolizumab combination therapy (instead of £5,576 per QALY) as a starting point.

Table 3: Deterministic/probabilistic EAG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Updated deterministic company base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£42,187	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,599	[redacted]	[redacted]
Matter of judgement (1-Subsequent treatments post selpercatinib based on LIBRETTO-001)							

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£46,693	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£11,273	[redacted]	[redacted]
Updated deterministic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£46,693	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£11,273	[redacted]	[redacted]
Updated probabilistic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£46,158	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£11,030	[redacted]	[redacted]

CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; iNMB = increment net monetary benefit; QALY = quality adjusted life year;

[1]ICER versus selpercatinib

[2]iNMB and iNHB for WTP of **£**36,000 per QALY

Table 4: Deterministic scenario analyses (conditional on updated EAG base-case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Deterministic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£46,693	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£11,273	[redacted]	[redacted]
Scenario analysis (Survival curves with highest NMB)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£43,032	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£9,711	[redacted]	[redacted]
Scenario analysis (Survival curves with lowest NMB)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£68,796	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,283	[redacted]	[redacted]
Scenario analysis (PF and PD utility based on TA654)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum	[redacted]	[redacted]	[redacted]	[redacted]	£46,937	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
chemotherapy							
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£11,327	[redacted]	[redacted]

EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; iNMB = increment net monetary benefit; NMB = net monetary benefit; PF = progression-free; PD = progressed disease; QALY = quality adjusted life year; TA = technology appraisal

[1]ICER versus selpercatinib

[2]iNMB and iNHB for WTP of **£**36,000 per QALY

1. REFERENCES

[1] Drilon A, Bergagnini I, Delasos L, Sabari J, Woo KM, Plodkowski A, et al. Clinical outcomes with pemetrexed-based systemic therapies in RET-rearranged lung cancers. Ann Oncol 2016; 27(7):1286-91

[2] Gray J, Rodríguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, et al. FP13.02 Pembrolizumab + Pemetrexed-Platinum vs Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189. Journal of Thoracic Oncology 2021; 16(3):S224

[3] National Institute for Health and Care Excellence. *Lung cancer: diagnosis and management. NICE guideline 122. Treatment pathways. Last updated: 22 September 2022 [Internet]*. London: National Institute for Health and Care Excellence, 2019 [accessed 29.9.22] Available from: https://www.nice.org.uk/guidance/ng122/resources/treatment-pathways-11189888173

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]

Technical Engagement response analyses – updated PAS

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC+)
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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Nigel Armstrong acted as project lead and health economist/review manager on this assessment, critiqued the clinical effectiveness methods and evidence and contributing to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Bram Ramaekers, Manuela Joore, Thomas Otten, Andrea Coves Fernandez and Teebah Abu-Zarah acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mark Perry acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Robert Wolff critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Table 1: Deterministic/probabilistic EAG base-case – updated selpercatinib PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Updated deterministic company base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,554	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	-£2,754	[redacted]	[redacted]
Matter of judgement (1-Subsequent treatments post selpercatinib based on LIBRETTO-001)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£40,060	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£2,920	[redacted]	[redacted]
Updated deterministic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£40,060	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£2,920	[redacted]	[redacted]
Updated probabilistic EAG base-case							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£39,880	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£2,787	[redacted]	[redacted]

CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; iNMB = increment net monetary benefit; QALY = quality adjusted life year;
[1]ICER versus selpercatinib
[2]iNMB and iNHB for WTP of **£**36,000 per QALY

Table 2: Deterministic scenario analyses - updated selpercatinib PAS

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Deterministic EAG base-case							

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER[1] (£/QALY)	iNMB[2]	iNHB[2]
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£40,060	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£2,920	[redacted]	[redacted]
Scenario analysis (Survival curves with highest NMB)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,992	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£1,876	[redacted]	[redacted]
Scenario analysis (Survival curves with lowest NMB)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£58,229	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	-£11,251	[redacted]	[redacted]
Scenario analysis (PF and PD utility based on TA654)							
Selpercatinib	[redacted]	[redacted]					
Pemetrexed + platinum chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£40,269	[redacted]	[redacted]
Pembrolizumab combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	£2,934	[redacted]	[redacted]

EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; iNMB = increment net monetary benefit; NMB = net monetary benefit; PF = progression-free; PD = progressed disease; QALY = quality adjusted life year; TA = technology appraisal

[1]ICER versus selpercatinib

[2]iNMB and iNHB for WTP of **£**36,000 per QALY

1. REFERENCES

[1] Drilon A, Bergagnini I, Delasos L, Sabari J, Woo KM, Plodkowski A, et al. Clinical outcomes with pemetrexed-based systemic therapies in RET-rearranged lung cancers. Ann Oncol 2016; 27(7):1286-91

[2] Gray J, Rodríguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, et al. FP13.02 Pembrolizumab + Pemetrexed-Platinum vs Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189. Journal of Thoracic Oncology 2021; 16(3):S224

[3] National Institute for Health and Care Excellence. *Lung cancer: diagnosis and management. NICE guideline 122. Treatment pathways. Last updated: 22 September 2022 [Internet]*. London: National Institute for Health and Care Excellence, 2019 [accessed 29.9.22] Available from: https://www.nice.org.uk/guidance/ng122/resources/treatment-pathways-11189888173

Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name: **Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer**
Topic ID: **4056**
Managed Access Lead: **Milena Wobbe**
Date of assessment(s): **09/10/2023**

Is Managed Access appropriate - Overall rating	Comments / Rationale
Yes	Although there are some key uncertainties that cannot be resolved through further data collection, some key uncertainties, namely the overall survival rates and progression-free survival rates, can be addressed with more mature trial (LIBRETTO-001) data. The next datacut date being considered by the company is commercial in confidence. Preliminary results from comparative RCT (LIBRETTO-431) could provide preliminary OS and PFS results at the end of 2023. Further data collected in clinical practice through SACT/Blueteq during a period of managed access may also validate the generalisability of the trial data to NHS clinical practice.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	Eligible for Cancer Drugs Fund
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Yes	The key uncertainties for this topic are the immaturity of the survival data both for selpercatinib (EAG12) but also for the comparator (EAG15). Both of these uncertainties could be resolved or significantly diminished with further data collection. Other uncertainties could only be resolved through further modelling and analysis from the company.
Can data collection be completed without undue burden on patients or the NHS system	Yes	Data collection would be routine, through ongoing trials or SACT
Are there any other substantive issues (excluding price) that are a barrier to a MAA	No	

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update	No	
pre-committee data collection working group	No	
pre-committee patient involvement meeting	No	

Key questions for committee if Managed Access is considered	
1	There is no timeframe proposed for exiting the CDF. The clinical trials run until 2024/25. Would this timeframe be sufficient to resolve the uncertainty relating to PFS and OS?
2	Is the model structure robust enough to make a decision at this time (see uncertainty EAG11)?

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the managed access.

Date agreed with NHSE	10/01/2023

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Yes	Selpercatinib is a candidate for the Cancer Drugs Fund (CDF). The currently available PFS and OS data available from the LIBRETTO-001 trial are immature, thus uncertainties in the evidence base could be resolved with further data collection. The company provided a Managed Access Proposal, although it lacks details on timeframes to exit.

IMF prioritisation criteria	Supporting Evidence
Potential to address a high unmet need	NSCLC is the third most common cancer in UK and has poor prognosis.
Potential to provide significant clinical benefits to patients	Early results indicating improved outcomes
represents a step-change in medicine for patients and clinicians	Yes - targeted for the RET gene mutation, and is first-in-class
new evidence could be generated that is meaningful and would sufficiently reduce uncertainty	See uncertainties section

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
High	Some uncertainties can be resolved through further data collection. Relevant data may be gathered in the two ongoing trials (LIBRETTO-001 and LIBRETTO-431), and also from SACT/Blueteq in clinical practice in the NHS. However, a number of uncertainties would not be resolved in this way and require further analyses by the company and/or committee judgement.

Key Uncertainties

Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes
EAG1	Population: uncertainty as to whether includes squamous histology	The company has not provided any evidence for the population with a squamous tumour histology, due to the trial inclusion/exclusion criteria	The relevant population should only be non-squamous histology	Unquantified	Evidence in the squamous population	SACT	Medium	SACT can capture squamous vs non-squamous for people treated with selpercatinib in clinical practice but this data might be immature.

EAG2	Comparators: mismatch to NICE scope and NICE guideline	Only included pemetrexed with platinum-based chemotherapy or pembrolizumab in combination with pemetrexed plus platinum chemotherapy. These are, according the clinical exerts consulted by the company, the only two relevant comparators. Mono-immunotherapies are, according to clinical experts, less effective and toxicity is high.	Include the following comparators, as per scope and NG122: - Pembrolizumab monotherapy - atezolizumab monotherapy - atezolizumab plus bevacizumab - carboplatin and paclitaxel - platinum doublet chemotherapy with or without pemetrexed maintenance treatment	Unquantified	Evidence that the omitted comparators are not being used in NHS clinical practice or evidence of selpercatinib's clinical effectiveness and cost-effectiveness versus those comparators	Discussion at ACM	No further data collection possible / proposed	This uncertainty could be resolved through expert evidence at committee.
EAG3	Subsequent therapy: possible bias resulting from mismatch between LIBRETTO-001 and NHS clinical practice	Uses cost effectiveness modelling as per assumed NHS practice, see explanation in EAG assumption.	The EAG has identified some discrepancies between the therapies used in the trials vs NHS clinical practice: - pemetrexed plus platinum chemotherapy: low use in trial vs assumed 70% in NHS - best supportive care: 0% in trial vs 20% assumed in NHS - pembrolizumab plus pemetrexed and platinum chemotherapy: 10-15% in trial vs 5% assumed in NHS. EAG supports basing the economic model on distribution that occurred during the clinical trial.	Low	Clarify the distribution of subsequent therapies in pivotal LIBRETTO-001 trial.	LIBRETTO-001 clinical trial	High	Company may resolve this ahead of ACM if it is able to clarify the distribution of subsequent therapies compared to EAG understanding. SACT would be able to gather this data in clinical practice.

EAG4	Lack of comparative evidence in the correct population	Preliminary results from LIBRETTO-001 are compared via an indirect treatment comparison with the outcomes of a permetrexed plus platinum chemotherapy single arm from another trial (KEYNOTE-189) and pembrolizumab with pemetrexed plus platinum chemotherapy via an NMA including three different trials, which are all mostly in RET fusion negative population.	Comparison between selpercatinib and the chosen comparators using a RTC in a RET fusion positive population	Low	Longer term data	LIBRETTO-431 trial	High	The ongoing RCT trial will gather relevant comparative data to resolve this uncertainty
EAG5	Applicability: there is no information on the characteristics of the UK target population	Did not include characteristics of the UK target population in the trial collection.	Asking for characteristics of the UK target population	Unquantified	Include data, such a "race" in the analysis to know whether or not race is an effect modifier. Include general characteristics of the UK target population.	Further evidence provision before ACM	No further data collection possible / proposed	This is likely to be in the trial data package already. Alternatively, the company should provide justification and evidence to explain why the data is generalisable to the UK target population.
EAG6	Adverse events: there are no specific adverse event data for the eligible participants relevant to the decision problem	Provided adverse events for the overall patient population in LIBRETTO-001 trial, which consists of 7 treatment arms, only one of which is of relevance here	Divide the data for adverse events up and allocate to the various treatment arms.	Unquantified	Adverse event data separated into the treatment arms / patient subgroups	LIBRETTO-001	No further data collection possible / proposed	This would show whether there is a greater concentration of adverse events in any subgroups than that observed overall. No further data collection necessary.
EAG7	ITC: choice of trial data (KEYNOTE-189) might have biased comparison with all comparators	Used KEYNOTE-189 trial (it allows access to individual patient data) data to establish a pseudo- comparator arm	Consider other sources of individual patient data to establish the pseudo-comparator arm (pemetrexed plus platinum chemotherapy), such as KEYNOTE-021	Unquantified	Other trial data	KEYNOTE-021 suggested by EAG	No further data collection possible / proposed	This could be resolved by further analysis ahead of ACM
EAG8	ITC: methods of adjustment for confounding might have biased comparison with all comparators	Used default PSM method to match pseudo-comparator arm to the selpercatinib arm	Addition of multivariate regression on the matched sample. Consideration of other covariates and selecting only RET fusion-positive comparator patients.	Low	N/A	Further evidence provision before ACM	No further data collection possible / proposed	This could be resolved by further analysis ahead of ACM

EAG9	NMA: heterogeneity in trials to inform pembrolizumab plus pemetrexed plus platinum chemotherapy versus pemetrexed plus platinum chemotherapy	Included KEYNOTE-189 Japan in the NMA.	Remove trial KEYNOTE-189 Japan and re-run analysis	Low	Re-analysis after removal of studies, e.g. KEYNOTE-189 Japan	Discussion at ACM	No further data collection possible / proposed	Requires committee judgement
EAG10	No NMA or comparative analysis was carried out for adverse events	No NMA analysis on adverse events	A comparison between selpercatinib and all comparators, including an NMA for adverse events	Unquantified	NMA or comparative analysis of adverse events	Further evidence provision before ACM	No further data collection possible / proposed	This could be resolved by further analysis ahead of ACM
EAG11	Model structure	Lack of a state transition model to assist in verifying the plausibility of partitioned survival model extrapolations and to address uncertainties in the extrapolation period	Compare the results of the partitioned survival model to the outcomes of a state transition model	High	Use of state transition modelling to assist in verifying the plausibility of partitioned survival model extrapolations	Further evidence provision before ACM	No further data collection possible / proposed	This could be resolved by further analysis ahead of ACM
EAG12	Immaturity of the data obtained from the LIBRETTO-001 trial for OS and PFS	The data obtained from the LIBRETTO-001 trial for OS and PFS are immature, adding substantial uncertainty to the extrapolated survival data in the economic model.	To reflect the uncertainty due to data immaturity, and resulting ambiguity in choice of survival curves, the EAG conducted scenario analyses to find the range of results given plausible parametric survival curves.	High	Longer term data (PFS & OS)	LIBRETTO-001	High	Longer-term data from the trial would reduce uncertainty
EAG13	The company's choice of survival curves for the modelling of treatment effectiveness was not transparent	Lack of transparency concerning the choice of survival curves for the modelling of treatment effectiveness	The EAG would like to see more information about a) the choice of considering complex survival curves, b) the plots that were not provided in the clarification response c) the choice between survival curves in detail and d) the mismatch between reported PFS and OS values in the CS and values used in the economic model.	Unquantified	N/A	Further evidence provision before ACM	No further data collection possible / proposed	This could be resolved by further analysis ahead of ACM

EAG14	Waning of the selpercatinib treatment effect was not explored.	The company did not explore waning of the selpercatinib treatment effect in the submission.	Hazard ratio plots for PFS and OS versus time to assess hazard ratios of selpercatinib versus comparators over time. An updated model and scenario analyses to explore the impact of treatment waning into the model.	Low	Hazard ratio plots for PFS and OS versus time to assess hazard ratios of selpercatinib versus comparators over time.	LIBRETTO-001	High	More mature data from the clinical trial should resolve uncertainty
EAG15	Company's estimated progression-free life years for pemetrexed plus platinum chemotherapy	The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses	Alternative approaches to estimate PFS for pemetrexed plus platinum chemotherapy where the modelled PFS > observed PFS for pemetrexed plus platinum chemotherapy.	High	Longer term data	LIBRETTO-001	High	Longer-term PFS data would improve the robustness of PSA and DSA carried out based on the observed results
EAG16	Health-related quality of life	The utility values from the company's base-case were higher than the ones used in other TAs, only slightly lower than the age and gender matched UK general population and had a small decrement between PF and PD states.	The EAG implemented the PD utility from TA654 in its base case	High	Longer term (PFS) data	Discussion at ACM	No further data collection possible / proposed	Requires committee judgement
EAG17	Resources and costs	Informed subsequent treatments post selpercatinib on experts contacted by company	Informing subsequent treatments post selpercatinib based on the LIBRETTO-001 trial. Informing subsequent treatments for the comparators based on NG122 and expert oncologist inputs.	High	Scenario analysis informing subsequent treatments post selpercatinib	SACT	High	More accurate understanding of subsequent therapies used in the NHS would improve the analysis of resources and costs. This can be refined based on committee discussion, and can be calculated based on evidence gathered in SACT.

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
High	RCT (LIBRETTO-431). Both trials are expected to be completed by mid-2025, with earlier datacuts available. This is within the timeframe for Managed Access, although the company have not provided a timeline for exiting the CDF. SACT/Blueteq can be used to obtain better insight into NHS clinical practice.

Clinical trial data - LIBRETTO-001	
Anticipated completion date	Sep-24
Link to clinicaltrial.gov	https://clinicaltrials.gov/ct2/show/NCT03157128
Start date	May-17
Data cut presented to committee	Jun-21
Link(s) to published data	https://pubmed.ncbi.nlm.nih.gov/32846060/ https://www.cancernetwork.com/view/libretto-001-trial-shows-promise-for-selpercatinib-in-nsclc-marked-by-ret-gene-fusions

Description of trial	Phase I-II open-label, multi-centre (including UK), single-arm trial (n=875 in total, but only small subgroup in this indication, n=39 for untreated in August 2020 data published above). There are 7 cohorts within this study, one of which is for people with NSCLC who are suitable for surgery and are followed up to five years after surgery. The eligible patient population is: "RET fusion positive early-stage non-small cell lung cancer (NSCLC) (histologically confirmed stage IB-IIIA NSCLC) participants who are candidates for definitive surgery. Participants will receive selpercatinib in a neoadjuvant and adjuvant setting. " This arm of the study is closed and no longer recruiting. The aim of the study is to evaluate the safety, tolerability, pharmacokinetics (PK) and preliminary anti-tumour activity, primarily measuring the maximum tolerated dose and objective response rate.

Clinical trial data - LIBRETTO-431	
Anticipated completion date	Aug-25
Link to clinicaltrial.gov	https://clinicaltrials.gov/ct2/show/study/NCT04194944
Start date	Feb-20
Data cut presented to committee	N/A
Link(s) to published data	https://www.jto.org/article/S1556-0864(21)00190-8/fulltext
Description of trial	Phase III open-label, multi-centre (including UK), randomised, controlled trial (n=250 expected) evaluating selpercatinib vs platinum-based and pemetrexed treatment +/- pembrolizumab in treatment-naïve patients with locally advanced or metastatic RET positive non-squamous NSCLC. Ratio is 2:1 for patients receiving selpercatinib vs standard care. Patients who are assigned the standard treatment have the option to potentially cross over to selpercatinib due to progressive disease on the standard treatment. The aim of the study is to measure selpercatinib clinical effectiveness vs standard treatment. The primary outcome measure is PFS.

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	**Rationale/comments**
High	This is an anti-cancer drug, with the primary data source being the ongoing clinical trials. The secondary data source could be the SACT dataset.

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Existing	NHS Digital's SACT dataset is an established mandatory dataset.
Prior experience with managed access	High	NHS Digital have extensive experience with managed access in the Cancer Drugs Fund
Relevance of existing data items	High	
If required, ease that new data items can be created / modified	Not applicable	No additional data items to be included
How quickly could the data collection be implemented	Normal timelines	SACT is an existing mandatory dataset. No additional time is required to implement data collection in clinical practice
Data quality		
Population coverage	High	SACT is an existing mandatory dataset that will capture the entire population treated with the medicine in clinical practice

Data completeness	High	NHS Digital have established processes in place to ensure high data completeness. Cohort of interest is identified by Blueteq records and NHS Digital follow-up with trusts where data is missing
Data accuracy	High	SACT is an established mandatory dataset and there is a good understanding of using SACT in clinical practice. NHS Digital have a dedicated help desk and follow-up with trusts where data submitted is ambiguous or lacks face validity
Data timeliness	High	Trusts submit records to the SACT dataset monthly
Quality assurance processes	Yes	Dedicated SACT data liaison officers and SACT helpdesk. Established process to ensure data quality available at: http://www.chemodataset.nhs.uk
Data availability lag	Low	Four months are required from data collection to allow for data to be uploaded to SACT, follow-up of missing data, and analysis and production of NHS Digital's report
Data sharing / linkage		
New data sharing arrangements required?	No	Data sharing agreements between NHSD, SACT, Blueteq and Personal Demographics Service (vital status) have been previously established
New data linkages required?	No	Data linkage has been previously established to allow NHSD to link Blueteq applications to SACT activity to identify the cohort of interest.
If yes, has the governance of data sharing been established	Not applicable	-
Analyses		
How easily could collected data be incorporated into an economic model	High	Individual-level patient data is available for the economic model. Subgroups of interest should be identified at the point of managed access entry so all relevant analyses can be produced.
Existing methodology to analyse data	Yes	Established methodology available here: http://www.chemodataset.nhs.uk
If no, is there a clear process to develop the statistical analysis plan	Not applicable	-
Existing analytical capacity	High	Established analytical capacity

Governance		
Lawful basis for data collection	Yes	6(1)e of the United Kingdom General Data Protection Regulations (UK GDPR). Statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021
Privacy notice & data subject rights	Not applicable	Mandated dataset as part of the Health and Social Care Information Standards
Territory of processing	Yes	UK
Data protection registration	Yes	
Security assurance	Yes	
Existing relevant ethics/research approvals	Not applicable	-
Patient consent	Yes	No prior patient consent required
Funding		
Existing funding	Yes	Established partnership between NHS England and NHS Digital
Additional funding required for MA	No	-
If yes, has additional funding been agreed in principle	Not applicable	-
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	No	Established mandatory dataset. No additional data items created
Are any of the clinical assessments not validated for use or accepted clinical practice	No	See above

HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	Data collection mandated by a Data Collection Agreement would be used for the purpose of the NICE guidance update
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	Established mandatory dataset. No additional data items created
Burden		
Additional patient burden	No	Existing mandated data set. No additional burden of data collection within managed access
Additional clinical burden	No	Existing mandated data set. No additional burden of data collection within managed access
Other additional burden	No	-

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
No	RET status testing would need to be incorporated into routine practice in order to ensure the relevant patients are offered the treatment, but this would not stop access to a MAA.

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	Low	Primary source of evidence generation is the clinical trial. Data collection in clinical practice through existing mandated data set. No additional burden of data collection within managed access.
	Expected overall additional system burden from data collection?	Low	As above

	Do stakeholders consider any additional burden to be acceptable	Not applicable	
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	Not applicable	

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?	No	No additional patient safety concerns identified
	Is there a clear plan to monitor patient safety within a MA?	Yes	No additional patient safety concerns identified
	Are additional patient safety monitoring processes required	No	No additional patient safety concerns identified

		Rating	Rationale / comments
Patient access after MAA	Will existing patients be able to continue to use the technology in the event of negative NICE guidance update	Yes	It the event of negative NICE guidance at the end of managed access it is expected, in line with principles of the Innovative drugs fund and Cancer Drugs Fund, that patients will continue to be able to receive the treatment until such time that the patient and the treating clinician determines it is no longer clinically appropriate.

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	No	RET status testing is available on the NHS but not currently part of routine practice/screening at the NHS Genomic Medicine Service. Next-generation screening panels could be adapted to include testing for RET fusions, when possible. Testing is available, as seen for the other selpercatinib topics in the CDF. Discussion at ACM will clarify this.

Implementation	Will implementation subject the NHS to irrecoverable costs?	No	It is unlikely that there will be irrecoverable costs, as this is already available.
	Is there an existing service specification which will cover the new treatment?	Yes	Selpercatinib and RET fusion screening available, even if not currently routinely offered.

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	It is expected that people with squamous and non-squamous histology would be eligible to access treatment, as occurred with the other selpercatinib topics in the CDF. Detailed Blueteq criteria will be developed by NHSE prior publication of any positive draft final NICE guidance.
	If yes, are these different to what would be used if the technology had been recommended for routine use?	No	Evidence was only provided for the population with non-squamous histology. This distinction is not made in the proposed MA wording. Previous selpercatinib topics (previously treated NSCLC and thyroid cancer) are part of the CDF without distinction of histology.

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	As above
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		

	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	
	Any issues from registry specific questions	No	

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	No	There is not expected to be any equality issues from a recommendation for use with managed access compared to a recommendation for routine use.

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	It is expected that a data collection agreement could be agreed within normal FAD development timelines (35 days) if committee make a recommendation for use in managed access. The company already have this technology in the CDF.